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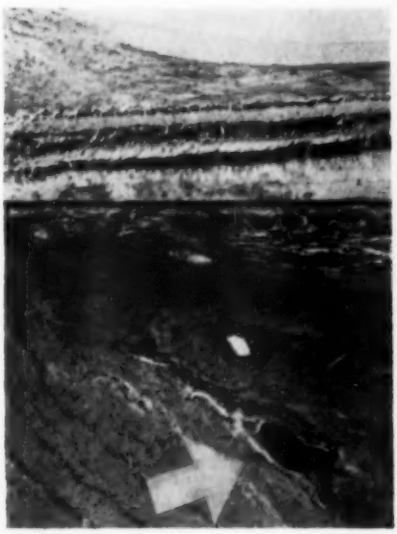

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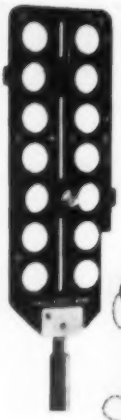

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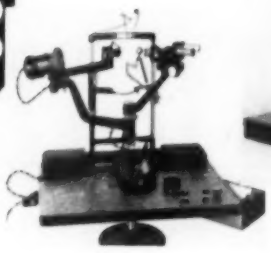

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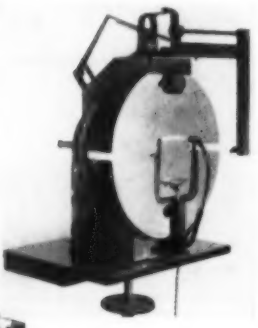

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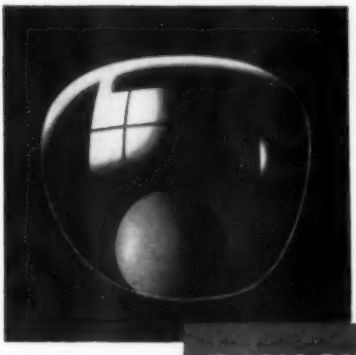

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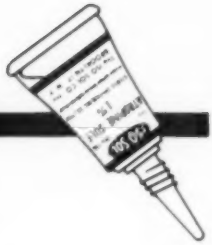

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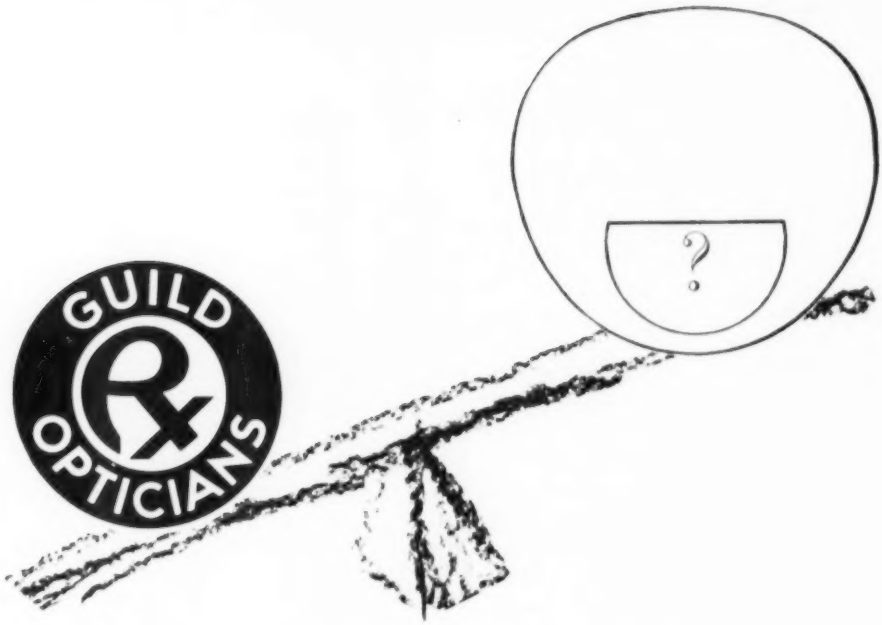

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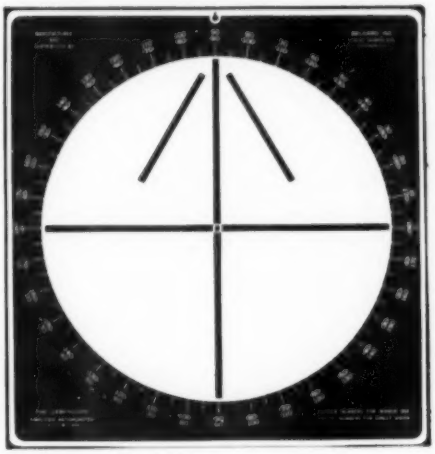

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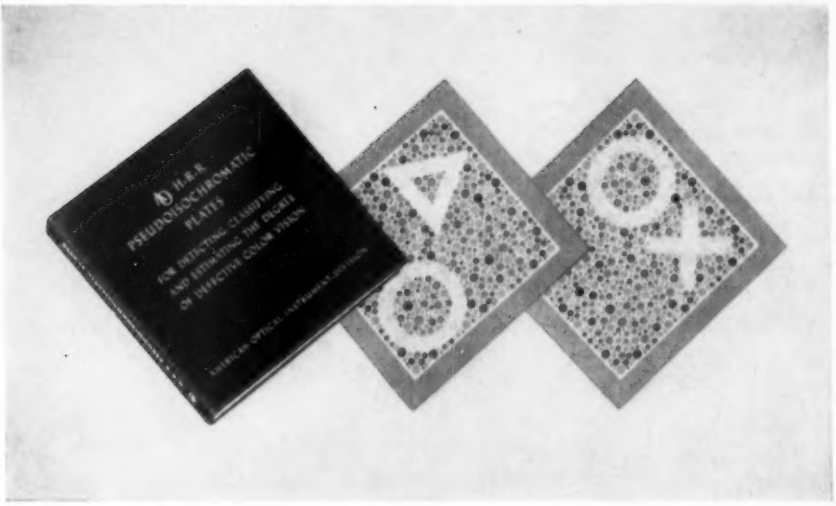

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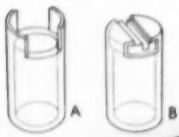

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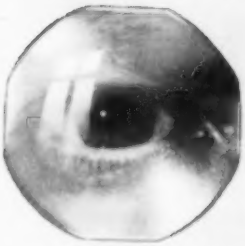

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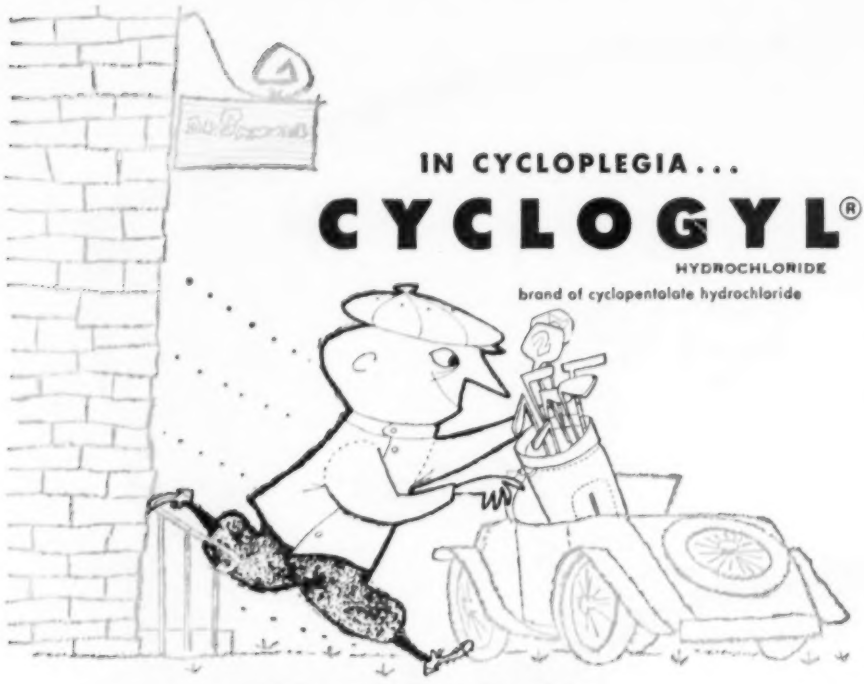

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*Successive drops at five-minute intervals.

†Recovery time reduced to six hours after one percent pilocarpine.

1. *Gordon, D. M., and Ehrenberg, M. H.: Am. J. Ophth. 38:831 (Dec.) 1954.*

"the chief handicap of maximum cycloplegia, namely its incapacitating effect, is minimized . . ."

Getter, B. C.: A.M.A. Arch. Ophth. 51:467 (Apr.) 1954.

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Ehrlich, L. H.: New York J. Med. 53:3013 (Dec. 15) 1953.

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Experimental Tonography

The Effect of the Carbonic Anhydrase Inhibitor Acetazoleamide on Aqueous Flow

BERNARD BECKER, M.D.
and
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The use of tonography for the measurement of absolute rate of aqueous flow is subject to a number of possible errors.[1] Many of these inaccuracies can be largely avoided when repeated tonography on the same eye is used for the evaluation of relative alterations in aqueous flow. Thus, in a series of 59 normal and glaucomatous eyes, repeated tonographic tracings before and three hours after oral acetazoleamide administration revealed an estimated average suppression of secretion of aqueous of 61%.*

Recently Kornblueth and Linnér † have presented evidence that tonography can be applied to rabbit eyes, using average values for ocular rigidity and corneal curvature. In the present investigation an attempt was made to quantitate the alteration in rabbit aqueous flow induced by carbonic anhydrase inhibition.

METHODS

Rabbits weighing 2-3 kg. were obtained from Haskins Rabbitry, St. Louis. In order to obtain a supply of "nonresponsive" rabbits, additional supplies were obtained from the Kresge Eye Institute, in Detroit, and from the Barkbridge Farms, Wenonah, N. J.

Tonography was caried out with an electronic tonometer. Tracings were made on a Leeds & Northrup recorder. All tonography was done with the rabbits under topical tetracaine (0.5%) anesthesia. By wrapping rabbits, the use of general anesthesia, as advocated by Kornblueth and Linnér, was avoided. Only those rabbits from which suitable tracings could be obtained were used.

Acetazoleamide (Diamox ‡) was administered as the sodium salt, 100 mg/kg., intravenously. All experiments were conducted so that there was an interval of approximately two hours between the two tonograms on the same eye. Acetazoleamide was administered 45 to 60 minutes before the second tonogram. Change in aqueous flow was calculated for rabbits by assuming a value of 9 mm. Hg for episcleral venous pressure.†

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From the Department of Ophthalmology, Washington University School of Medicine, and the Oscar Johnson Institute.

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* Becker, B.: Evaluation of Glaucoma Therapy by Tonography, presented at the International Congress of Ophthalmology, New York, Sept. 21, 1954.

† Kornblueth, W., and Linnér, E., paper presented at the meeting of the Wilmer Residents Association, Baltimore, April, 1955.

‡ Supplied through the courtesy of Dr. James D. Gallagher, Clinical Research Section, Lederle Laboratories Division, American Cyanamid Company, Pearl River, N. Y.

Thus,

$$\Delta F\% = 100\frac{(P_2-9)C_2-(P_1-9)C_1}{(P_1-9)C_1}$$

where

P_1 = intraocular pressure before acetazoleamide
C_1 = facility of outflow before acetazoleamide
P_2 = intraocular pressure after acetazoleamide
C_2 = facility of outflow after acetazoleamide
$\Delta F\%$ = per cent change in flow of aqueous

TABLE 1.—*Tonography in Rabbits*

Rabbit No.		Before Acetazoleamide		After Acetazoleamide (45-60 Min.)		
		P_1	C_1	P_2	C_2	$\Delta F\%$
4	OD	22	0.17	14	0.14	−68
	OS	20	0.18	14	0.18	−55
5	OS	29	0.18	16	0.10	−64
12	OD	25	0.18	15	0.20	−58
	OS	25	0.20	17	0.13	−68
13	OD	24	0.15	17	0.12	−54
	OS	24	0.11	13	0.20	−52
126	OD	22	0.19	13	0.15	−70
	OS	28	0.30	20	0.13	−75
129	OD	24	0.15	13	0.15	−73
	OS	20	0.16	17	0.13	−62
153	OD	24	0.16	18	0.10	−63
	OS	24	0.17	13	0.15	−76
159*	OD	36	0.08	33	0.03	−67
	OS	42	0.09	38	0.05	−51
161	OD	27	0.28	18	0.26	−54
	OS	24	0.26	19	0.15	−62
167	OS	22	0.40	16	0.25	−66
168	OD	24	0.17	22	0.08	−59
	OS	22	0.19	22	0.08	−58
174	OD	28	0.20	18	0.16	−62
	OS	28	0.20	17	0.20	−58
177	OS	20	0.20	17	0.11	−60
209	OS	20	0.20	17	0.18	−64
211	OD	28	0.20	16	0.19	−77
	OS	26	0.28	15	0.20	−75
212	OD	31	0.15	16	0.10	−79
213	OD	24	0.16	17	0.10	−73
	OS	20	0.18	17	0.09	−63
226	OD	21	0.22	14	0.20	−62
	OS	20	0.21	14	0.18	−59
242	OD	16	0.20	16	0.07	−65
	OS	17	0.20	15	0.11	−59
245	OS	24	0.15	16	0.16	−50
257	OD	24	0.15	17	0.13	−54
	OS	24	0.15	17	0.13	−54
258	OD	32	0.38	21	0.33	−55
	OS	36	0.33	17	0.30	−73
259	OD	30	0.42	20	0.39	−62
	OS	36	0.43	19	0.37	−68
261	OD	31	0.20	20	0.14	−65
	OS	26	0.20	18	0.15	−60
262	OS	24	0.20	15	0.20	−60
271	OD	28	0.19	22	0.13	−52
	OS	28	0.20	20	0.13	−63
312	OD	25	0.22	20	0.14	−56
	OS	28	0.20	22	0.15	−49
313	OD	26	0.12	16	0.10	−67
314	OD	26	0.20	16	0.20	−63
	OS	31	0.24	15	0.20	−77
				Mean (50 eyes)		−63%
				S. D.		± 8%

$$\Delta F\% = 100\frac{(P_2-9)C_2-(P_1-9)C_1}{(P_1-9)C_1}$$

P_1 = intraocular pressure before acetazoleamide
P_2 = intraocular pressure after acetazoleamide
C_1 = facility of outflow before acetazoleamide
C_2 = facility of outflow after acetazoleamide

* Rabbit 159 subsequently developed progressive glaucoma in both eyes with further decrease in facility of outflow and rise in intraocular pressure, leading to enlarged globes with steamy cornea.

RESULTS

In a series of 50 eyes, systemic inhibition of carbonic anhydrase resulted in an average suppression of flow of 63% (Table 1). In some rabbit eyes intraocular pressure was lowered without change in facility of outflow (Figs. 1-4). In other rabbits it was apparent that compensatory decreases in facility of outflow maintained intraocular pressure in spite of similar decreases in aqueous flow (Figs. 5, 6). All variations between these two extremes were noted and are recorded in Table 1. Moreover, in almost all rabbits tonography at intervals of three to six hours after acetazoleamide revealed that restoration of intraocular pressure was accomplished primarily by a decreased facility of outflow before aqueous flow had returned to normal.

COMMENT

The average decrease of aqueous flow of 63% found by tonography in rabbits is quite consistent with the alterations in composition of the ocular fluids induced by acetazoleamide. By comparing steady-state concentrations of bicarbonate and ascorbate in the posterior and anterior chamber fluids of rabbit eyes before and after carbonic anhydrase inhibition, estimates were obtained for changes in aqueous flow.[2] Thus, the posterior chamber concentration of bicarbonate decreased from a mean of 68% excess over plasma level to 38% excess. Anterior chamber bicarbonate averaged 36% in excess of plasma level and fell after acetazoleamide to 10% above plasma level. These bicarbonate data were found to be consistent with an average suppression of aqueous flow of 64%. Similar comparisons of steady-state concentrations of ascorbic acid in the posterior and anterior chamber fluids suggested an average of 60% inhibition of secretion of aqueous humor.

The decrease in aqueous flow as determined by repeated tonography on the eyes of patients was also found to be in excellent agreement with the data for rabbits. Effects of the same magnitude have resulted from fluorescein-appearance-time studies in rabbits

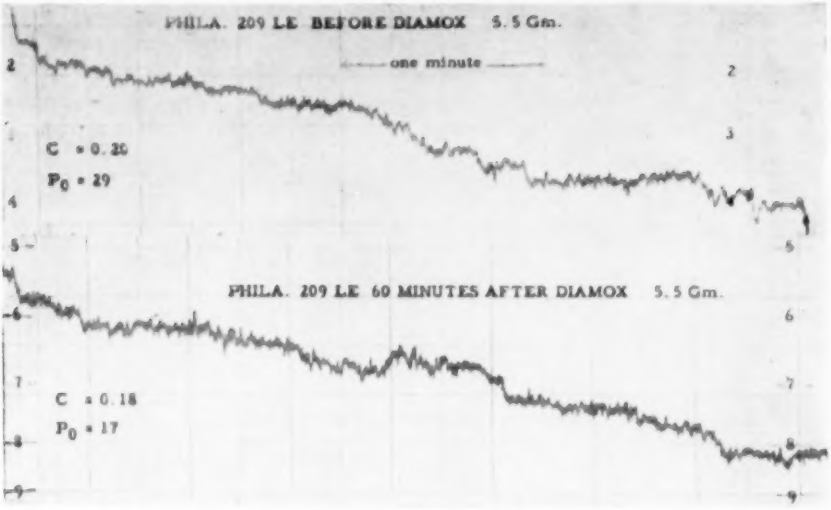
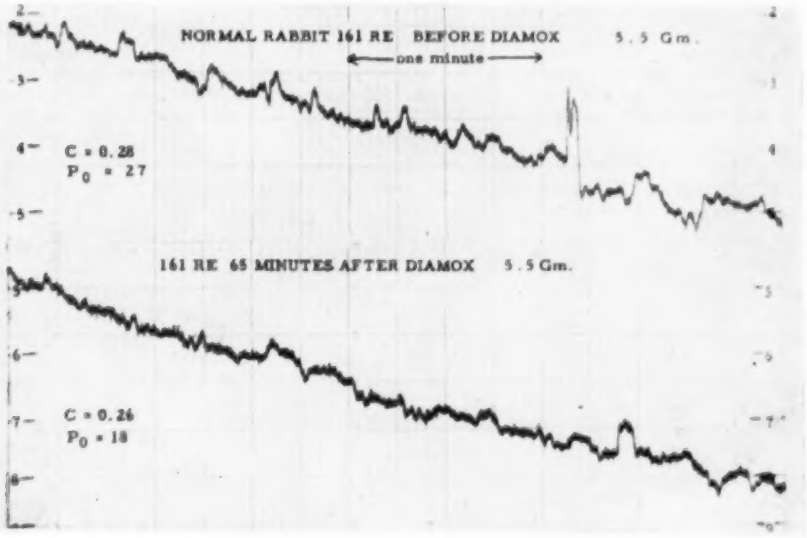


Fig. 1.—"Responsive" rabbit (No. 209).

Repeated tonographic tracings on a rabbit eye one hour before (above) and one hour after (below) the intravenous administration of acetazoleamide (100 mg/kg.). Note the fall in intraocular pressure (P_0) without significant change in facility of outflow (C).

Fig. 2.—"Responsive" rabbit (No. 161).

Tonographic tracings, rabbit eye, before (above) and after (below) the systemic administration of acetazoleamide (100 mg/kg. intravenously), illustrating a fall in intraocular pressure (P_0) with little change in facility of outflow (C).



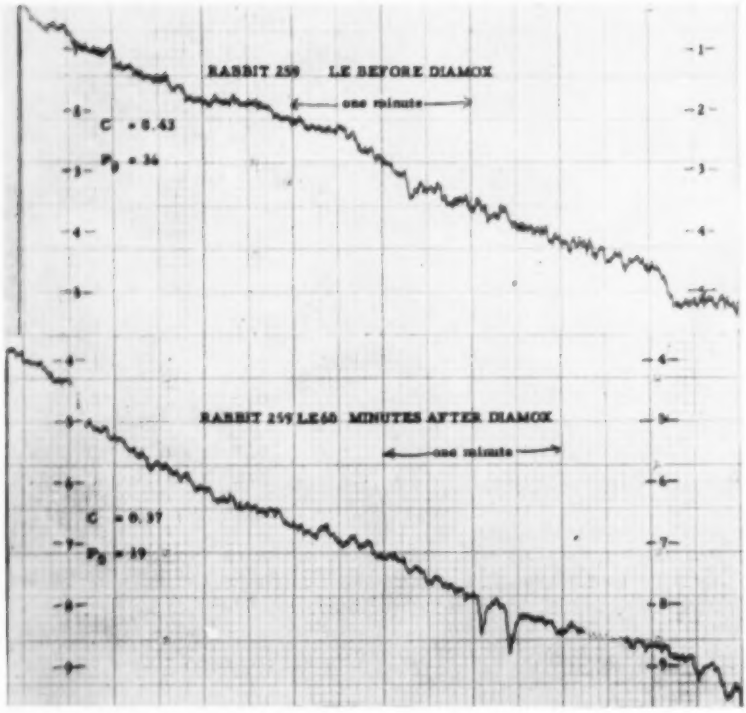
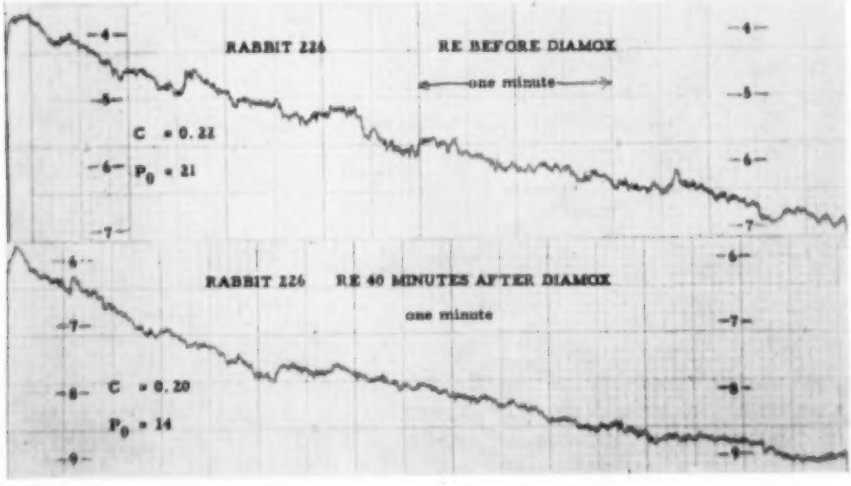


Fig. 3.—"Responsive" rabbit (No. 259).
Tonographic tracings, rabbit eye, before (above) and after (below) the systemic administration of acetazoleamide (100 mg/kg. intravenously), illustrating a fall in intraocular pressure (P_0) with little change in facility of outflow (C).

Fig. 4.—"Responsive" rabbit (No. 226).
Tonographic tracings, rabbit eye, before (above) and after (below) the systemic administration of acetazoleamide (100 mg/kg. intravenously), illustrating a fall in intraocular pressure (P_0) with little change in facility of outflow (C).



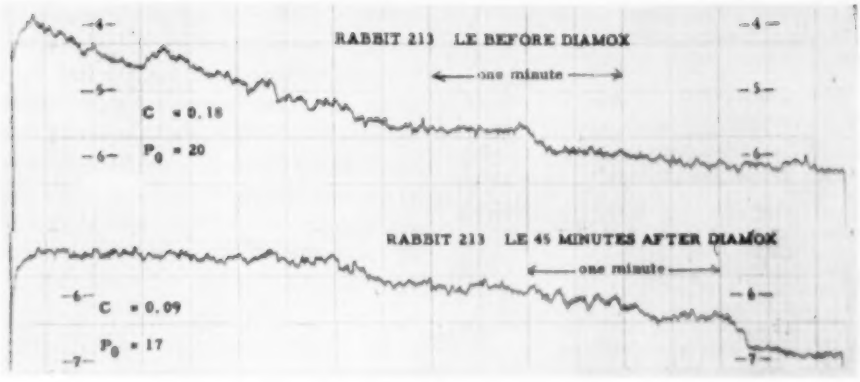


Fig. 5.—"Pseudoresistant" rabbit (No. 213).

Tonographic tracings before (above) and after (below) the systemic administration of acetazoleamide (100 mg/kg. intravenously), demonstrating a compensatory decrease in facility of outflow (C), resulting in little fall in intraocular pressure (P_0) in spite of suppression of secretion.

and patients § and from ascorbic-acid-turnover determinations in rabbits.‖ A summary of the changes in flow induced by acetazoleamide as measured by various methods is presented in Table 2. This comparison can be carried one step further by comparing tonography and bicarbonate steady-state data on the same animal before and after acetazoleamide (Table 3). Here, the agreement between the two methods is even closer than when different animals are compared.

It is apparent that several very different approaches to the problem of measuring acetazoleamide-induced changes in aqueous flow yield strikingly similar results. This increases confidence in the methods of measurement and the assumptions and approxima-

§ Becker, B.: Evaluation of Glaucoma Therapy by Tonography, presented at the International Congress of Ophthalmology, New York, Sept. 21, 1954.

‖ Becker, B.: Unpublished data.

Fig. 6.—"Pseudoresistant" rabbit (No. 177).

Tonographic tracings before (above) and after (below) the systemic administration of acetazoleamide (100 mg/kg. intravenously), demonstrating a compensatory decrease in facility of outflow (C), resulting in little fall in intraocular pressure (P_0) in spite of suppression of secretion.

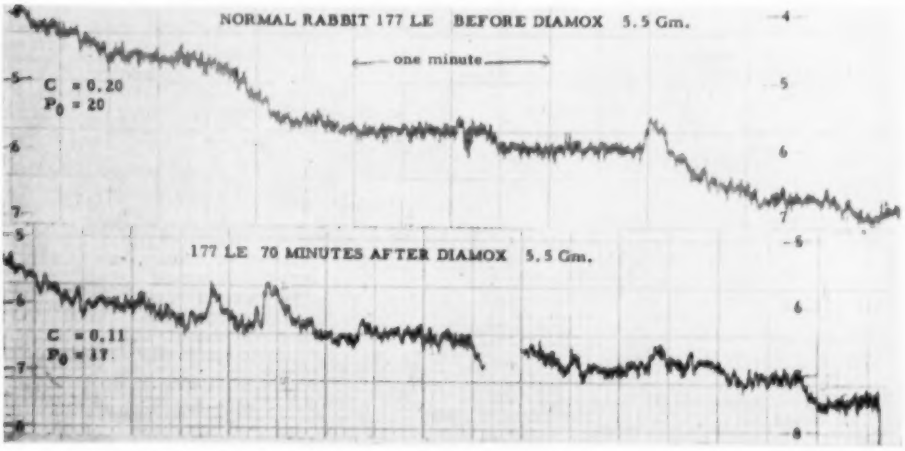


TABLE 2.—*Summary of Changes in Aqueous Flow Following Carbonic Anhydrase Inhibition*

Method	No. Eyes	Change in Flow
Steady-state rabbits *		
Bicarbonate	30	−64%
Ascorbic acid	28	−60%
Saturated ascorbic acid	15	−51%
Tonography*		
Rabbits	50	−63%
Patients	50	−61%
Fluorescein-appearance time *		
Rabbits	11	−44%
Patients	12	−42%
Ascorbic acid turnover †	—	−52%

* Becker, B.: Evaluation of Glaucoma Therapy by Tonography, presented at the International Congress of Ophthalmology, New York, Sept. 21, 1954.
† Becker, B.: Unpublished data.

tions involved in each. It also establishes a reasonably accurate estimation of the effects of this carbonic anhydrase inhibitor on the rate of formation of aqueous humor.

One result of these studies has been the obvious inadequacy of evaluating responsiveness of rabbits by measurements of intraocular pressure alone. This point has been emphasized repeatedly in the evaluation of patient response to acetazoleamide.¶ The true pharmacologic response of patients, as well as rabbits, can only be estimated by evaluating facility of outflow as well as intraocular pressure.

It is also clear from Table 1 that the so-called "unresponsiveness" of most rabbits in Detroit, Philadelphia, and elsewhere does not result from a failure to suppress aqueous flow by carbonic anhydrase inhibition. This "pseudoresistance" merely represents an ability of the animal's eye to maintain intraocular pressure, in spite of the decreased inflow of aqueous, by a compensatory shutting down of the outflow mechanism (Figs. 5, 6). It should be noted that 33 of the 50 eyes in Table 1 would be classified as "nonresponsive" (pseudoresistant) if a 3-scale-unit change of the tonometer is defined as "response." Furthermore, 14 eyes failed to change by at least 2 scale units, and 5 eyes changed less than 1 scale unit. However, all these eyes had comparable inhibitions of aqueous flow.

These findings afford an explanation for the similarity of changes in posterior chamber and anterior chamber chemistry in both "responsive" and "pseudoresistant" rabbits.# It is also understandable that no differences were found in the concentration of carbonic anhydrase and acetazoleamide in the ciliary

¶ Becker, B.: The Short-Term Administration of Diamox in the Therapy of the Glaucomas, presented at the International Congress of Ophthalmology, New York, Sept. 20, 1954.

Becker, B.: Personal observations, 1954.

TABLE 3.—*Comparison of Tonography and Steady-State Bicarbonate Changes Induced by Acetazoleamide*

Rabbit 161

Bicarbonate (mM/L)		Tonography	OD	OS
C_{PI_1}	= 24.8	P_1 = 27	24	
C_{PC_1}	= 44.8	C_1 = 0.28	0.26	
C_{AC_1}	= 33.5			
C_{PI_2}	= 20.0	P_2 = ?	19	
C_{PC_2}	= 30.8	C_2 =	0.15	
C_{AC_2}	= 22.7			
ΔF_{HCO_3}%	= −57%	ΔF_1% = −54%	−62%	

C_{PI} = plasma concentration
C_{PC} = posterior chamber concentration
C_{AC} = anterior chamber concentration
ΔF_{HCO_3}% = per cent change in aqueous flow calculated from

$$\frac{K_F}{K_D} = \frac{C_{AC} - C_{PI}}{C_{PC} - C_{AC}}$$

assuming no change in K_D, the diffusion coefficient

Rabbit 211

Bicarbonate (mM/L)		Tonography	OD	OS
C_{PI_1}	= 25.4	P_1 = 28	26	
C_{PC_1}	= 37.3	C_1 = 0.30	0.28	
C_{AC_1}	= 32.5			
C_{PI_2}	= 19.9	P_2 = 16	15	
C_{PC_2}	= 31.5	C_2 = 0.19	0.20	
C_{AC_2}	= 22.9			
ΔF_{HCO_3}%	= −75%	ΔF_1% = −77%	−75%	

P = intraocular pressure (mm. Hg)
C = facility of outflow
1 = before acetazoleamide
2 = after acetazoleamide
ΔF_1% = per cent change in aqueous flow assuming episcleral venous pressure 9 mm. Hg

processes of both these groups of animals.* Furthermore, the finding of Green and associates [3] of a failure of acetazoleamide to lower intraocular pressure in some rabbits is confirmed, but does not justify their conclusion that carbonic anhydrase inhibition does not affect aqueous secretion.

The systemic acidosis and sodium loss induced by carbonic anhydrase inhibition led to speculation about possible stimulation of the adrenal cortex of responsive rabbits. The increase in plasma glucose and fall in plasma lactate in rabbits following acetazoleamide administration were consistent with such a hypothesis.† The role of steroids in the responsiveness of rabbit eyes to acetazoleamide appeared worthy of exploration. Preliminary data indicate that the systemic administration to rabbits of corticotropin or some adrenal steroids, most especially fludrocortisone (9α-fluorohydrocortisone) prevents the compensatory decrease in outflow facility following acetazoleamide. Thus, these steroids convert "pseudoresistant" rabbits to the "responsive" state. However, tonographic evidence suggests that changes of aqueous flow induced by acetazoleamide are not altered significantly by this type of steroid administration. Further studies are in progress to determine the effects of adrenal steroids on facility of outflow and compensatory mechanisms of intraocular pressure regulation.

It is of considerable interest that even maximum carbonic anhydrase inhibition in the rabbit and man results in only some 50% to 60% suppression of aqueous flow. This is perhaps best interpreted as indicating that the uncatalyzed reaction of hydration and dehydration of carbon dioxide is sufficiently rapid in the ciliary body to permit 40%-50% of normal secretion to take place in the absence of carbonic anhydrase.

Clinically, the uncatalyzed residual rate of secretion provides important regulatory factors in the administration of acetazoleamide. On the one hand, it limits the amount of decrease in intraocular pressure that can be achieved therapeutically with acetazoleamide. On the other hand, the residual flow may be the important factor that has permitted long-term carbonic anhydrase inhibition without significant toxicity to the lens or other ocular structures.‡

Consistent with the thesis of a residual rate of aqueous secretion which is not dependent upon the enzyme carbonic anhydrase is the failure further to depress aqueous flow by even tenfold increases in dose of acetazoleamide. Additional evidence for this hypothesis is provided by the administration of acetazoleamide to selected patients with spontaneous decrease in aqueous flow (Table 4). It is apparent that eyes with aqueous flow of less than 1 cc. per minute do not respond to acetazoleamide as dramatically as do eyes with higher flow rates. In fact, some of these eyes do not respond at all (e. g., Patient

TABLE 4.—*Effect of 500 Mg. of Acetazoleamide on Seventeen Eyes with Open-Angle Glaucoma and "Decreased Aqueous Flow"* *

Patient	Eye	P_1	C_1	P_2	C_2	$\Delta F\%$
S. K.	OD	26	0.03	19	0.04	−25
	OS	26	0.05	16	0.05	−40
B. J.	OD	15	0.09	13	0.10	−35
	OS	13	0.11	12	0.10	−33
L. B.	OD	23	0.05	19	0.06	−18
	OS	20	0.07	18	0.06	−31
W. S.	OD	30	0.09	20	0.07	−22
C. T.	OD	17	0.03	16	0.03	−14
	OS	15	0.04	15	0.04	0
F. W.	OS	18	0.06	16	0.07	−12
N. R.	OS	25	0.06	24	0.06	− 7
O. B.	OD	28	0.01	30	0.01	− 7
	OS	25	0.00	24	0.00	0
M. M.	OD	24	0.04	22	0.05	+ 7
	OS	25	0.04	21	0.05	− 8
R. L.	OD	22	0.02	19	0.03	+12
	OS	25	0.02	21	0.03	+10
					Mean =	−13%
					S. D. =	±16%

* $(P_1 = 10)$ $C < 1.0$
P_1 = intraocular pressure before acetazoleamide
P_2 = intraocular pressure after acetazoleamide
C_1 = facility of outflow before acetazoleamide
C_2 = facility of outflow after acetazoleamide
$\Delta F\%$ = per cent change in flow of aqueous
Episcleral venous pressure assumed as 10 mm. Hg

* Ballintine, E. J., and Maren, T. H.: Carbonic Anhydrase Activity and the Distribution of Diamox in the Rabbit Eye, presented at the meeting of the Association for Research in Ophthalmology, Atlantic City, N. J., June 8, 1955.

† Becker, B.: Personal observations, 1954.

‡ References 4 and 5.

R. L., in Table 4). A similar resistance to acetazoleamide is seen in a few rabbit eyes with spontaneously depressed rates of secretion (Fig. 7). Such eyes are refractory to the drug, as to its effects on both flow and intraocular pressure.

It is important to emphasize that the suppression of aqueous flow by acetazoleamide lasts much longer than does the depression of intraocular pressure in many responsive rabbits and in a number of patients. Thus, the initial effect of the oral administration of 500 mg. of acetazoleamide upon normal human eyes was a fall in intraocular pressure to a minimum in two to four hours without intraocular pressure in spite of persistent suppression of secretion of aqueous. One must appreciate that such animals with compensated reduced flow were relatively resistant to repeated acetazoleamide. Therefore, it has proved unwise to administer carbonic anhydrase inhibitors or other potential inhibitors of aqueous flow during the days preceding an experiment (or to space repeated acetazoleamide experiments too close together). From the clinical point of view, some of the refractory states that develop from the infrequent administration of acetazoleamide may be explained by such compensatory mechanisms.

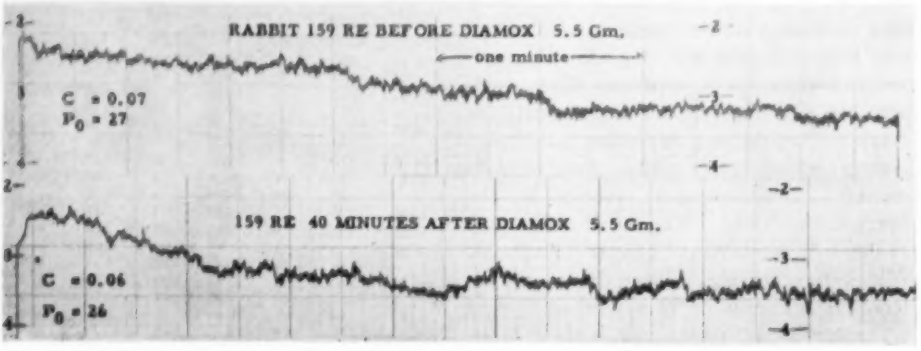


Fig. 7.—"Refractory" rabbit (No. 159).

Tonographic tracings before (above) and after (below) systemic acetazoleamide (100 mg/kg. intravenously), illustrating the failure to alter intraocular pressure (P_0), facility of outflow (C), or aqueous flow in an eye exhibiting spontaneously decreased aqueous secretion.

significant change in facility of outflow.§ However, the restoration of intraocular pressure in some of these eyes 6 to 24 hours later was accomplished partly by an increase in resistance to outflow.‖ Subsequently, aqueous flow and the outflow facility became normalized. Similarly, in responsive rabbits, intraocular pressure often returned to normal by two to three hours after intravenous acetazoleamide administration, but this also represented a compensatory restoration of

§ Becker, B.: Evaluation of Glaucoma Therapy by Tonography, presented at the International Congress of Ophthalmology, New York, Sept. 21, 1954.

‖ Becker, B.: Personal observations, 1954.

SUMMARY

1. Repeated tonographic tracings on 50 rabbit eyes indicate that systemic carbonic anhydrase inhibition results in an average of 63% (±8%) suppression of aqueous secretion. This estimate of suppression of aqueous flow induced by acetazoleamide is in good agreement with measured alterations in steady-state chemistry, turnover of test substances, and fluorescein-appearance time.

2. The remaining 35%-40% of the normal aqueous flow cannot be inhibited even by massive doses of acetazoleamide. Some eyes which exhibit only this reduced rate of flow appear to be refractory to carbonic anhydrase

inhibitors, *as to their effects both on intraocular pressure and on aqueous flow.*

3. In some rabbit eyes the decreased inflow of aqueous humor following acetazoleamide is associated with a compensatory decreased facility of outflow, resulting in little fall in intraocular pressure ("pseudoresistance"). Such rabbits are "nonresponsive" to acetazoleamide *only in terms of fall of intraocular pressure*, for they do exhibit similar pharmacologic suppression of aqueous humor formation to that found in "responsive" rabbits. The administration of adrenal steroids, such as fludrocortisone, can prevent the compensatory decrease in facility of outflow in these eyes, thus permitting a fall in intraocular pressure following acetazoleamide administration.

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Isoniazid and Ocular Tuberculosis

An Evaluation of Experimental and Clinical Studies

WILLIAM H. KRATKA, M.D., Wilmington, Del.

Isoniazid (isonicotinic acid hydrazide, known by the trade names of Nydrazid and I. N. H.) first attained prominence in the literature in 1952, at which time multiple studies were reported on its effectiveness, experimentally and clinically, in the therapy of pulmonary and other forms of tuberculosis.*

Isoniazid is a white, crystalline solid, freely soluble in water at any pH. It is poorly soluble in the common inert organic solvents, such as ethanol, ether, and benzene. In a dry state and in neutral and acid aqueous solutions, it is stable at room temperatures. Biological fluids, feces, and aqueous solutions containing isoniazid can be autoclaved for one hour at 15 lb. of pressure without destruction of the isoniazid in them provided the material is made acid before heating.[16]

Submitted for publication May 3, 1955.

The Research Department of the Phipps Institute supplied cultures of tubercle bacilli, and E. R. Squibb & Sons supplied the isoniazid (Hydrazid) used.

Mr. John Sawyer, biochemist in the Research Department, aided in the carrying out of the intricate tissue and chemical studies involved in these experiments.

All the experimental studies here reported were done in the Research Department of the Wills Eye Hospital, in Philadelphia, and the major portion of the patients treated were inpatients at the Wills Eye Hospital. This study was made in partial fulfilment of requirements for the degree of Master of Medical Science. Dr. Irving H. Leopold, director of the Research Department, gave guidance, direction, and assistance in the conduct of the many phases of these studies, without which it would have been impossible to complete them.

* E. R. Squibb & Sons, Institute for Medical Research, unpublished data from Research and Developmental Laboratories, 1952. References 1 to 15.

From the reports [16] on toxicity studies in several species of animals, it has been shown that both isoniazid and its isopropyl derivatives are of relatively low toxicity in doses which appear to be effective therapeutically. These drugs were mainly excreted in the urine and within one hour or so following administration were well distributed throughout the body (blood serum, cerebrospinal fluid, pleural fluid).

The maximum doses tolerated experimentally in mice, rats, and dogs agree with the doses calculated on the basis of relative body surface area. These amounts are approximately 64, 40, and 10 mg. per kilogram per day. Conversion of these calculated doses to man suggested a maximum dose of 4 to 5 mg. per kilogram per day.[17]

It was found [18] that maximum amounts of isonicotinic acid hydrazide and 1-isonicotinyl-2-isopropylhydrazine were in the plasma within 1½ to 2 hours after oral administration, but no significant amounts were present after 24 hours. These levels were determined by the colorimetric method.

The following experimental studies were started at the Research Department of Wills Eye Hospital in 1952. They were performed on nonallergic, nonimmune rabbits in an attempt to evaluate the effectiveness of this drug in the treatment of tuberculosis of the eye.

TOXICITY STUDIES OF ISONIAZID IN RABBITS

Methods and Results

1. *Topical applications.*—*(a)* Drops: One drop of sterile aqueous solutions containing varying concentrations of isoniazid (10, 20, 30, 50, 75, and 100 mg.) per cubic milliliter was applied to the eyes of different groups of rabbits either every 10 minutes or every hour, with no observable irritating effects.

(*b*) Ointment: Ointment concentrations of 100 and 200 mg. of isoniazid per gram of petrolatum base were applied three times a day to the eyes of another group of rabbits. This resulted in moderate conjunctival and lid irritation, which disappeared in 24 hours upon discontinuance of therapy.

2. Subconjunctival Injections.—One group of six rabbits received subconjunctival injections containing 10 mg. of isoniazid per injection, and a second group of six rabbits were given injections containing 20 mg. per dose. No local irritation or systemic ill-effects following these injections were noted in any of the rabbits of either group.

3. Intramuscular Injections.—In this experiment two groups of six rabbits each were again used. The first group received 10 mg., and the second 20 mg., of isoniazid per kilogram of body weight injected intramuscularly. These doses averaged from 18 to 36 mg. per day. No immediate local irritation was evident, but after repeated injections at the same site some secondary fibrosis was noted.

4. Oral Therapy.—To two groups of rabbits of six each, isoniazid was administered by tuberculin syringe after being dissolved in 10 cc. of water. One group was given 10 mg., and the second group 20 mg., per kilogram of body weight per day. No toxic effects, such as gastrointestinal upsets, weight loss, urinary retention or frequency, or disturbances of the central nervous system, were observed.

PENETRATION STUDIES OF ISONIAZID IN RABBITS

Assay Methods

The procedure is based upon the extraction of isoniazid from basic solutions into a 20% isoamyl alcohol-ether-ammonium sulfate system, reextraction into acid, and subsequent determination, either spectrophotometrically or colorimetrically. The colorimetric method which was used in performing the animal studies and in determinations in the following experiments has a lower limit of reliability in plasma or urine at concentrations of about 1γ/ml. The spectrophotometric method, using the ultraviolet absorption peak at 266 mμ, is reliable at concentrations of about 5γ/ml. The Klett-Summerson photoelectric colorimeter was used to make the determinations. (Assay methods for isoniazid applicable to biological fluids were developed in the Research and Developmental Laboratories of E. R. Squibb & Sons).

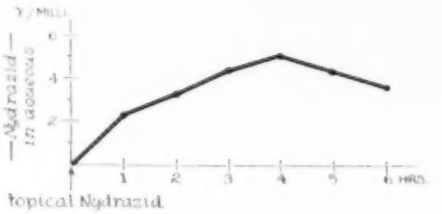


Fig. 1.—Anterior chamber penetration: aqueous isoniazid (100 mg. per milliliter), 1 drop topically every hour.

Observations

1. *Anterior Chamber Studies* (10 rabbits in each group).—(*a*) Topical Application: 1. Drops. One drop, containing 100 mg. of isoniazid per milliliter was applied every hour to the conjunctival cul-de-sacs for four consecutive hours. (The isoniazid used was dissolved in sterile distilled water slightly acidified with N/10 HCl and autoclaved.) Colorimetric determinations were then made on the aqueous fluid withdrawn from the anterior chamber every hour for six hours. The greatest concentration (5γ) was noted at the end of the fourth hour (Fig. 1).

2. Ointments. An ointment containing 200 mg. of isoniazid per gram of petrolatum base was applied once daily to the conjunctiva of another group of rabbits. Quantitative determinations were then made on aqueous fluid withdrawn every two hours for six hours. This resulted in a peak concentration of 30γ of isoniazid following application (Fig. 2).

(*b*) Subconjunctival Injection: For comparison, two groups of rabbits were injected

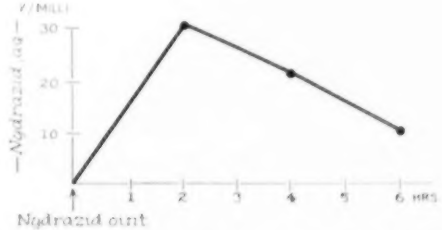


Fig. 2.—Anterior chamber penetration: isoniazid ointment (200 mg. per gram).

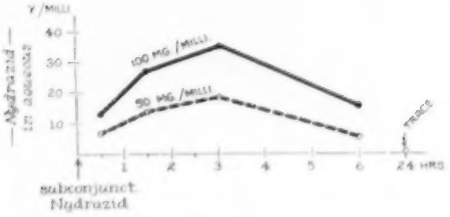


Fig. 3.—Anterior chamber penetration following 0.2 cc. of isoniazid given conjunctivally. Heavy line: 100 mg. per milliliter; broken line: 50 mg. per milliliter; total doses 20 and 10 mg., respectively.

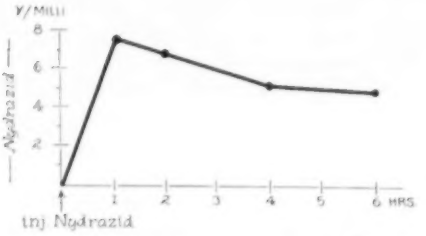


Fig. 5.—Anterior chamber penetration following intramuscular isoniazid (20 mg. per kilogram of body weight).

subconjunctivally. The first group was given 20 mg., and the second group 10 mg., per injection. At the end of three hours the first group showed 3.5γ per milliliter, and the second group 1.5.5γ per milliliter. At the end of six hours concentrations of 1.6γ and 7γ per milliliter were present in the two groups respectively (Fig. 3).

(*c*) Oral Therapy: Again, comparative studies were made with two sets of rabbits. One set was given a single dose of 20 mg. of isoniazid per kilogram of body weight every 24 hours. The second set was given 20 mg. also, but it was divided into 10 mg. doses given twice in 24 hours. In these studies a peak of 9γ was noted in the single-dose method, as compared with a 7γ peak in the divided-dose method. Note in Figure 4, of this experiment, that the repeated doses of smaller amounts were more effective over a 24-hour period.

(*d*) Intramuscular Injections: Each rabbit in this group was given a single intramuscular injection of isoniazid (20 mg. per kilogram). The highest concentration of the drug (7.5γ per milliliter) was found in the anterior chamber at the end of the first hour. At the end of six hours an average of 5γ was still present (Fig. 5).

(NOTE: The eyes of all rabbits used in these experiments were irrigated with sterile nitromersol [Metaphen] solution, 1:10,000, prior to the use of isoniazid. Topical akinesia was maintained with 0.5% tetracaine hydrochloride. All aqueous withdrawals were performed with a sterile 26-gauge needle on a tuberculin syringe. All enucleations were done with the animal under anesthesia, and the rabbits were killed by means of intravenous air injections.)

Summary of Anterior Chamber Penetration Studies: The studies described above demonstrated the following facts:

1. All methods of administration of isoniazid produced adequate concentrations in the anterior chamber.

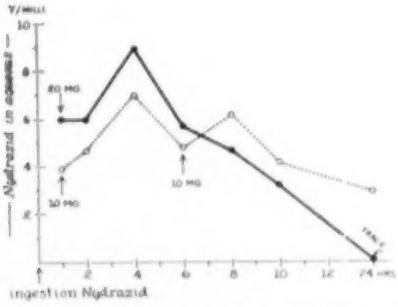


Fig. 4.—Comparative isoniazid penetration studies of the anterior chamber with single and divided dosage.

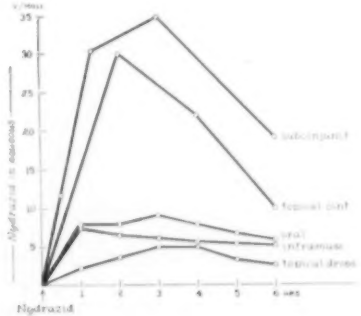


Fig. 6.—Comparative isoniazid penetration studies of the anterior chamber.

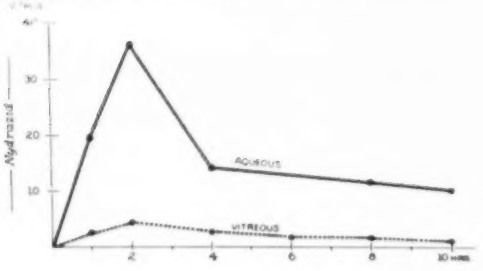


Fig. 7.—Isoniazid penetration studies of the aqueous and vitreous humors by topical ointment (200 mg. per gram).

2. Maintenance of adequate concentration is better achieved by repeated smaller doses than by larger single doses over a period of 24 hours.

3. The most effective methods of therapy in the anterior chamber were (1) subconjunctival injections and (2) topical ointment applications.

2. *Vitreous Penetration Studies* (six rabbits in each group).—(*a*) Topical Ointment Application: After topical application of isoniazid ointment (200 mg. per gram) comparative studies were made of the concentrations found in the vitreous and in the aqueous of the same eyes. In the vitreous, a peak of 2γ per milliliter was reached in 2 hours, and 1.1γ per milliliter was still present at the end of 10 hours. In the aqueous, a peak of 30γ was reached in 1 hour and 10γ was still present at the end of 10 hours (Fig. 7).

(*b*) Intramuscular Injections: In this group, intramuscular injections (20 mg. per kilogram) were given in single daily doses. Comparative studies were again made of the concentrations found in the aqueous and vitreous of the same animals. Peak levels of 20γ in the aqueous and of 5.2γ in the vitreous were reached one hour following the injection (Fig. 8).

Summary of and Conclusions on Comparative Studies of Aqueous and Vitreous Penetration: Adequate penetration was achieved in the vitreous by both topical and intramuscular methods of therapy.

A higher concentration was found in the vitreous after the intramuscular injections than after topical application.

Topical application resulted in a higher concentration in the aqueous than in the vitreous.

Topical therapy with isoniazid is more effective in the treatment of anterior segment pathology.

Systemic administration of isoniazid is more effective in the treatment of posterior segment pathology.

Higher concentrations in the vitreous resulted from better penetration through the blood-aqueous barriers than by the indirect topical method of therapy.

3. Isoniazid Penetration of Ocular Tissues.—Isoniazid ointment (200 mg. per gram) was applied topically to a new group of rabbits. Dry-weight determinations at the end of two hours showed an average concentration of 15.4γ in the cornea and 3.8γ in the combined scleral-retinal sections. At the end of four hours, an average of 10γ was present in the cornea and of 2.0γ in the scleral-retinal sections (Fig. 9). From these studies we have found that isoniazid penetrates all ocular tissues rapidly and in adequate concentrations. In vitro studies have demonstrated its bacteriostatic proper-

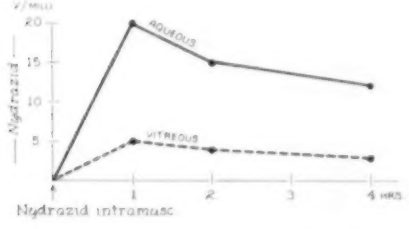


Fig. 8.—Isoniazid penetration studies of the aqueous and vitreous humors by intramuscular administration (20 mg. per kilogram).

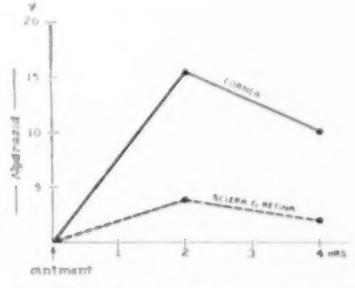


Fig. 9.—Isoniazid penetration studies of ocular tissues by topical ointment (200 mg. per gram).

ties against Mycobacterium tuberculosis (H37Rv) in concentrations as low as 0.02γ to 0.06γ per milliliter.

ISONIAZID AGAINST NONTUBERCULOUS ORGANISMS

In vitro studies [16] have shown that insoniazid has a narrow antibacterial spectrum. It is ineffective in vitro against the common Gram-negative and Gram-positive pathogenic bacteria. It is also ineffective against certain protozoa and the influenza virus in mice. It may possess some slight antifungal properties [2] and is under investigation as to its effectiveness against other organisms and diseases.

Studies were done with preparations of (1) Pseudomonas aeruginosa (Pyocyaneus) and (2) Staphylococcus aureus to determine the effectiveness of isoniazid against nontuberculous organisms in rabbit eyes. These organisms were prepared in the following manner:

> After centrifugation of a pure 18-hour trypticase-soy broth culture of a strain of P. aeruginosa, the supernatant fluid was decanted and sterile isotonic solution of sodium chloride was added to the packed organisms. The organisms were then dispersed evenly throughout the solution. Once more the organisms were centrifuged and the supernatant fluid decanted. Enough sterile isotonic solution of sodium chloride was added to the packed organisms that the final nephelometer reading of the suspended bacteria was 600,000 per cubic centimeter of sterile isotonic solution of sodium chloride. These sterile suspensions of cultures were checked by smear and culture of solutions for contaminations prior to injection.[18]

One group of six rabbits was given injections intracorneally and also into the anterior chamber of 0.1 cc. of a suspension of P. aeruginosa (600,000 per cubic centimeter). A second group of six rabbits received injections of S. aureus in the same concentration into the cornea and into the anterior chamber. Despite the use of isoniazid topically every hour of the day plus isoniazid intramuscularly once every 24 hours, all rabbits developed hypopyon and buphthalmos within 24 hours. Thus it was shown that isoniazid was totally ineffective in the above-mentioned infection of the eyes.

ISONIAZID AGAINST TOXIC KERATITIS

Topical applications with pure pellets of sodium hydroxide, reagent grade, were made to the central apical areas of the cornea of six rabbits to induce localized toxic keratitis. This procedure was followed by topical application of isoniazid four times a day (24 hours) for six days. At the end of this treatment no greater improvement was seen in this group than in a control group treated topically with isotonic saline solution. It was therefore concluded that this drug has no value in induced toxic keratitis.

ISONIAZID AGAINST TUBERCULOUS KERATITIS AND UVEITIS

I. *Intracorneal Tuberculosis* (Bovine bacilli).—The rabbits were divided into two groups of 10 each. One-tenth cubic centimeter of a preparation† containing 150 bovine bacilli per oil immersion field was injected into the corneas of all rabbits. This resulted in edematous corneal blebs ranging from 5 to 7 mm. in width. Initial activity was noted in eight to nine days in the form of small satellite projections appearing at the margins of the blebs. At the end of 14 to 16 days two principal changes were noted: (1) an increase in the vascular supply at the limbal margin proximal to the site of injection in the cornea, and (2) moderate to severe iris edema and prominence of the iris markings. In approximately 50% of the rabbits both changes were present.

From the 15th to the 20th day following inoculations, all the control rabbits showed a gradual increase in size of the central infiltrated areas. A large number of the lesions progressed to epithelial necrosis and ulceration plus increased limbal vascularization and pannus formation. (Control rabbits received no therapy except daily lavage of the cul-de-sacs with 1:10,000 nitromersol.‡

From the 28th to the 35th day most of the eyes showed hypopyon formation in the anterior chamber plus a generalized spread of the corneal infiltrated areas. By the 50th to the 60th day all eyes showed severe central corneal necrosis, panophthalmitis, and

buphthalmos. Some of the globes perforated at this stage (Fig. 13).

Treatment with Isoniazid: The rabbits to be treated were divided into two groups of five each. One group was injected intramuscularly with 20 mg. of isoniazid per kilogram of body weight once every 24 hours. The second group received the same intramuscular injection plus topical isoniazid drops every 12 hours (100 mg. per milliliter).

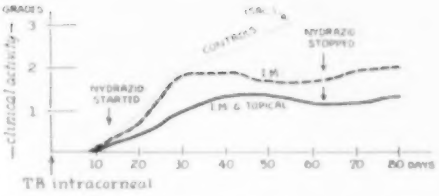


Fig. 10.—Intracorneal studies—bovine tubercle bacilli, 150 organisms per oil immersion field; treated with intramuscular and topical isoniazid.

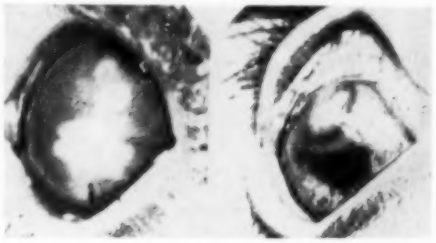
The first treated group (intramuscular) showed practically the same degree of inflammatory changes as the control group for the first 20 days. However, from about the 28th to the 30th day there was a definite leveling of activity at the Grade 2 degree clinically.

The second treated group (intramuscular and topical) showed a more marked improvement from therapy, maintaining a low Grade 2 level.

Treatment was stopped on both groups after 53 days. This resulted in a gradual increase in clinical activity during the next 14 days. At this time both groups of treated rabbits were killed.

Laboratory Studies: Ziehl-Neelsen stains and Petragnani-agar cultures were made of all control and treated eyes, and all were found to be positive for tuberculous organisms and pathologic changes. However, the

Fig. 11.—Left, control; right, treated eye. Sixteen days of isoniazid therapy (topical and intramuscular).



† Preparation of Tubercle Bacillus Suspensions: Young cultures of tubercle bacilli of the human type (H37Rv) and of the bovine type (Ravenel) were grown on a modified Lowenstein medium. These cultures were ground in an agate-smooth mortar with the aid of a few drops of bile. The mixtures were then suspended by the addition of a 0.15 M sodium biphosphate (sodium acid phosphate) solution to contain approximately 10 mg. per milliliter.[19]

The suspensions were then treated in either of two ways: 1. Slow centrifugation for one minute, followed by filtration of a 1:10 dilution of the supernatant fluid through one or two layers of Whatman #5 paper to remove the clumps. This yielded a suspension in which the majority of the micro-organisms were present as isolated cells but which still contained up to 5% of clumps, containing 20 or more micro-organisms. 2. Centrifugation of similar suspensions containing approximately 10 mg. per milliliter at 2000 revolutions per minute for five minutes, followed by filtration of the supernatant fluid through a sterile sintered glass filter of medium porosity at a negative pressure of 2 to 3 lb. per square inch. This method yielded suspensions in which most of the micro-organisms were present as isolated cells, and only occasionally could groups of three to six bacteria be found. At no time were there large clumps, such as those found after filtration through Whatman #5 filter paper.

The opacity of the suspensions described above was now determined in a Klett-Summerson photoelectric colorimeter. Following this colorimetric standardization, a sterilized platinum loop spread of the above suspensions in oil immersion field was microscopically checked and adjusted by dilution to give the desired number of tubercle bacilli.

Note: In Figures 10, 13, 14, and 18 to 20 clinical activity was divided as follows:

Grade 1: Corneal edema with or without iris swelling and plasmoid-like aqueous

Grade 2: (*a*) Intracorneal group: corneal necrosis, ulceration, and vascularization

(*b*) Anterior uveitis group: iris tubercles and early hypopyon formation

Grade 3: Anterior chamber suppuration plus marked iris infiltration and vascularization

Grade 4: Panophthalmitis and buphthalmus with or without perforation

‡ References 21 and 22.

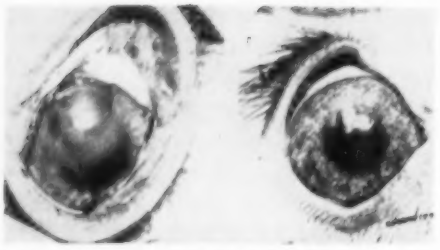


Fig. 12.—Left, control; right, treated eye. Thirty-five days of isoniazid therapy. Note decrease in size of corneal bleb and marked clinical improvement of anterior of anterior chamber in treated eye.

treated group showed fewer organisms and less extensive pathologic changes. Inflammatory changes and infiltration in these globes were limited to the anterior two-thirds of the cornea, whereas in the nontreated group these changes frequently extended into the angles of the anterior chamber.

Conclusions: 1. Clinical studies showed isoniazid to be of bacteriostatic value in the treatment of intracorneal tuberculosis in that there was a reduction in clinical activity during treatment and an increase in activity with the cessation of therapy.

2. Pathologic studies showed that isoniazid exerted some bacteriostatic effects by the decreased number of organisms present and by the reduced amount of tissue changes in the treated globes, despite the large inoculations used in these experiments.

II. *Anterior Chamber Tuberculosis* (Bovine Bacilli).—Again, the rabbits were divided into two groups of 10 each, one for control and one for treatment. One-tenth cubic centimeter of a similar preparation

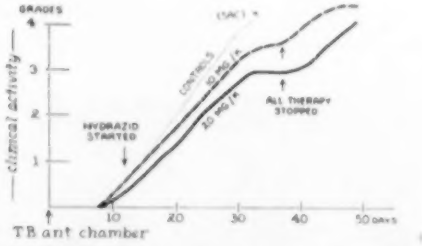


Fig. 13.—Anterior chamber penetration studies: bovine tubercle bacilli; 150 organisms per oil immersion field; treated with intramuscular isoniazid (20 mg. per kilogram).

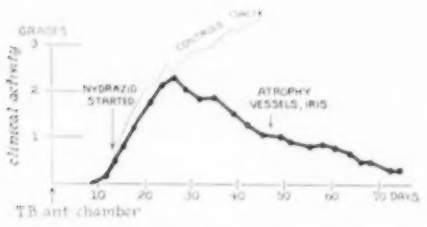
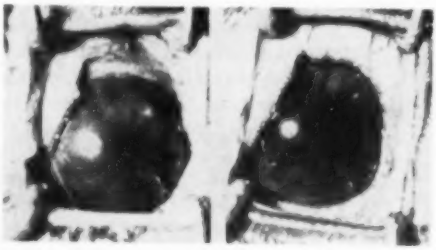


Fig. 14.—Anterior chamber penetration studies: bovine tubercle studies (3 to 5 organisms per oil immersion field); treated with intramuscular isoniazid (20 mg. per kilogram).

(150 organisms per oil immersion field) was injected into the anterior chambers of all the rabbits. On the 8th to the 10th day, iris edema and a cloudy-like, plasmoid aqueous was noted. By the 20th to the 25th day, all eyes showed hypopyon formation and the presence of an inflammatory plastic exudate over the anterior surface of the lens. From the 28th day on, all globes showed increasing iritis, tubercle formation, and suppuration in the anterior chamber. The nontreated (control) eyes developed generalized enlargement, panophthalmitis, and frequent perforation.

Treated Eyes: The rabbits to be treated were divided into two groups of five each. The first group was given 10 mg. of isoniazid, and the second group 20 mg., intramuscularly every 24 hours. Both these groups showed only slight benefit from therapy, as compared with the control group, up to the 20th day (Fig. 13). From the 20th to the 30th day the controls rapidly progressed to Grade 4 activity and were destroyed. On the other hand, the uveitis in the treated animals mostly remained at Grade 3 until

Fig. 15.—Anterior chamber tuberculosis. Left, control; right, treated eye. Twelve days of isoniazid therapy (intramuscular).



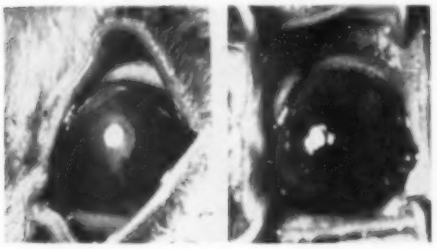


Fig. 16.—Anterior chamber tuberculosis. Left, control; right, treated eye. Thirty days of isoniazid therapy.

the 35th day, at which time all therapy was stopped. Within two weeks all eyes progressed to Grade 4 uveitis.

Laboratory Studies: With use of the Ziehl-Neelsen stain for microscopic smears and Petragnani-agar media for cultures, both control and treated groups showed the presence of tuberculous organisms. Histologic sections showed typical tuberculous changes, i. e., cellular infiltration and necrosis, tubercles with giant cell activity in the iris and ciliary bodies, and occasional involvement of the anterior choroidal segments of the globe. Some sections showed secondary inflammatory glaucomatous changes, due to the occlusion of the filtration angle and a deep cupping of the disc.

Conclusions: 1. In the laboratory studies the treated rabbits demonstrated a reduction in number of organisms and inflammatory changes as compared with the controls.

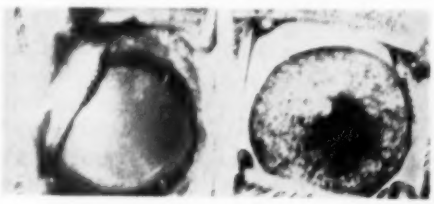
2. Clinically there was noted a moderate, but definite, improvement in the treated rabbits, showing that isoniazid does have some therapeutic value despite the very large inoculations used.

III. *Action of Isoniazid Against Tuberculous Uveitis* (3 to 5 organisms per oil immersion field).—Therapy Started Eight Days After Inoculation: In this experiment, the rabbits were divided into two groups of 10 each, one for control and one for treatment. All rabbits in both groups were inoculated with 0.1 cc. of a suspension of tubercle bacilli (3 to 5 organisms per oil immersion field) in the anterior chambers. Intramuscular injections of 20 mg. of isoniazid per kilogram were started on the eighth day in one group. There was little, if any, difference in the amount of inflammatory change noted in the two groups until the 25th day (17 days of therapy). From the 25th to the 45th day the treated group showed a marked decline in tuberculous activity, whereas the uveitis in the controls rapidly progressed to Grade 4 activity and the animals were killed. Treatment was continued in the first group up to the 75th day following the original inoculations, after which the only evidence of previous inflammation noted was iris atrophy and some areas of increased iris vascularity.

Laboratory studies. Smears, cultures, and sections of the globes of the controls showed marked tuberculous involvement of the anterior segments, extending well back into the filtration angles and the overlying sclera. The treated rabbits showed negative smears and cultures, with only a moderate degree of inflammatory involvement of the iris and ciliary bodies plus some atrophy of the iris stroma.

Conclusions. From this series of experiments, it appears that isoniazid has definite bacteriostatic, and possibly bactericidal, effects in milder tuberculous infections in the anterior chamber (3 to 5 organisms per oil immersion field), in that (1) the pathologic changes found in the treated eyes were considerably less than those found in the nontreated eyes, (2) definite clinical improvement followed about 21 days of therapy, (3) after 70 days of therapy all clinical activity had ceased, and (4) laboratory studies were negative for tubercle bacilli and showed only low-grade inflammatory activity.

Fig. 17.—Anterior chamber tuberculosis. Left, control; right, treated eye. Sixty-five days of isoniazid therapy. Note marked improvement in treated eye, as compared with control.



Therapy Started Third Day Following Inoculation: Procedures in this experiment were identical with those of the previous one except that isoniazid therapy was started on the third day following the inoculations (3 to 5 organisms per oil immersion field). At this time there was no evidence of any clinical changes. However, on the eighth day rapid inflammatory changes took place in both groups of rabbits. By the 45th day the control rabbits had advanced to Grade 4 clinically and were killed. The treated group showed moderate improvement up to the 45th day (42 days of therapy). From this time on clinical improvement was more rapid, and by the 75th day inflammation had declined to low Grade 1 levels of activity. These rabbits were then killed for pathologic studies.

Laboratory studies showed negative smears and only one questionably positive culture. Histologic sections showed a limited amount of inflammatory change, similar to that in the treated rabbits in the previous experiment.

From this experiment, one can conclude that earlier use of isoniazid failed to produce any dramatic improvement, and it was again necessary to continue treatment for at least four to five weeks before any marked improvement took place. Despite prolonged therapy, the presence of low-grade inflammatory changes and questionably positive cultures brings out the possibility of resistant organisms to this drug. Again, it was evident that two to three months of isoniazid therapy is required to bring about any definite clinically favorable results.

COMPARATIVE EFFECTIVENESS OF ANTITUBERCULOUS DRUGS

Bovine Bacilli

A. Isoniazid Versus Streptomycin-Para-aminosalicylic Acid.—Three groups of rabbits, of 10 each, were inoculated with bovine bacilli (3 to 5 organisms per oil immersion field) in the anterior chambers. Therapy was started three days later, as follows: Group I received 20 mg. of isoniazid per kilogram per day; Group II received 50 mg. of streptomycin and 500 mg. of PAS per kilogram per day; Group III acted as the nontreated controls (Fig. 18).

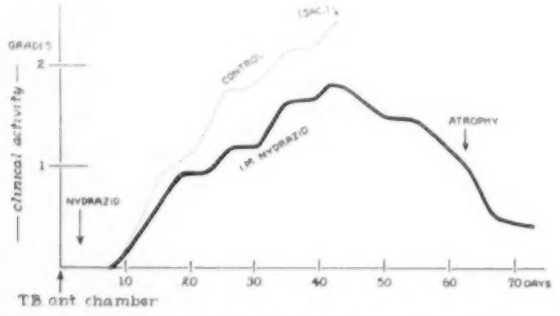


Fig. 18.—Anterior chamber penetration studies. Bovine tubercle bacilli (3 to 5 organisms per oil immersion field); treated with intramuscular isoniazid (20 mg. per kilogram).

All three groups showed early clinical activity, with the control group reaching Grade 4 level within 35 days. At this time both treated groups had reached Grade 3, with slightly less activity present in the isoniazid group.

B. Isoniazid Plus Streptomycin-PAS.—On the 45th day, in view of the increasing activity in the streptomycin-PAS group, daily isoniazid therapy was added. From this time on both groups showed a steady decline in inflammation, with the streptomycin-PAS group reaching Grade 2, and the isoniazid group reaching Grade 1, by the 80th day (Fig. 19).

C. Conclusions.—1. Both these antituberculous medications have therapeutic value,

with isoniazid producing earlier clinical improvement.

2. Addition of isoniazid to streptomycin and PAS proved more effective, due either to drug synergism or to the combined ability of the drugs to destroy more resistant organisms.

3. Two to three months of therapy was necessary to produce satisfactory clinical improvement.

Human Bacilli

Using human bacilli (H37Rv), 3 to 5 organisms per oil immersion field, and repeating the same inoculations and antituberculous therapy of the preceding experiment with bovine bacilli, similar clinical results were obtained (Fig. 20). Once more, isoniazid produced earlier improvement, and the combined use of the drugs was more effective than the use of the streptomycin-PAS alone.

Conclusion from Experimental Studies with Isoniazid

Toxicity.—Isoniazid is a relatively nontoxic agent [42] and, aside from rare and preventable side-effects, can be administered with safety topically, orally, or parenterally over prolonged periods.

Penetration.—Isoniazid shows excellent qualities of penetration into all the ocular tissues. This penetration is best achieved in the anterior segment by topical application and in the posterior segment of the globe by oral or parenteral administration.

Therapeutic Spectrum.—Isoniazid has a very narrow spectrum of antibacterial action.[42] In these experiments it appeared to have no therapeutic value in toxic or bacterial keratitis.

Therapeutic Value.—Isoniazid displays definite bacteriostatic, and possibly bactericidal, properties in the treatment of tuberculous ocular lesions in nonimmune, nonallergic rabbits.

Comparison with Other Antituberculous Drugs.—Isoniazid demonstrated an earlier and more effective therapeutic value in comparison with streptomycin and paraaminosalicylic acid.

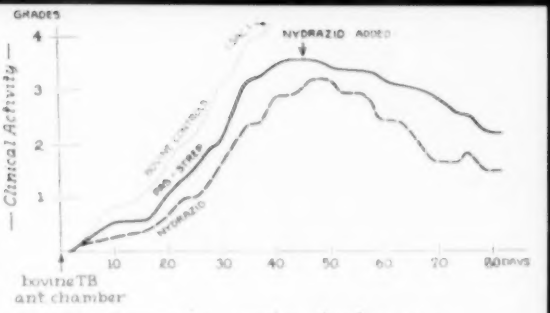


Fig. 19.—Comparative anterior chamber penetration studies with bovine tubercle bacilli (3 to 5 organisms per oil immersion field); treated with isoniazid plus PAS and streptomycin.

Synergism.—Isoniazid combined with streptomycin and paraaminosalicylic acid showed greater effectiveness against experimental tuberculous lesions in preventing a recurrence in clinical and pathologic activity.

On the basis of these experiments, it appears that isoniazid is a therapeutic agent worthy of consideration in the treatment of tuberculous lesions of the eye. Results indicate that clinical improvement should begin within two to four weeks from the onset of therapy. However, to eliminate all tissue activity, as well as all bacterial activity, it is evident that therapy must be continued for a minimum of four months. The presence of resistant strains of the tubercle bacillus is strongly suggested, as noted by Woods,[44] both in the synergistic effect observed when isoniazid is added to streptomycin and paraaminosalicylic acid and also in the recurrence of activity following cessation of isoniazid before sufficient therapy was given.

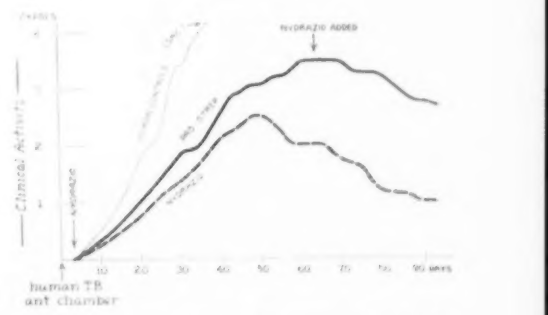


Fig. 20.—Anterior chamber penetration studies with human tubercle bacilli (2 to 5 organisms per oil immersion field); treated with intramuscular isoniazid (20 mg. per kilogram), as compared with PAS (500 mg. per kilogram) and streptomycin (50 mg. per kilogram).

CLINICAL EVALUATION OF ISONIAZID IN OCULAR TUBERCULOSIS

A. Diagnostic Survey.—In this clinical study, in order to determine whether or not a lesion was tuberculous in origin, the following laboratory studies were made:

1. Routine tests
   - (*a*) Tuberculin skin tests
   - (*b*) Wassermann test
   - (*c*) Brucella skin and agglutination tests
   - (*d*) Serum albumin-globulin ratio
   - (*e*) Urinalysis
   - (*f*) Complete blood count
2. Additional studies where indicated
   - (*a*) X-rays of chest, sinuses, and extremities
   - (*b*) Uveal pigment and lens sensitivity skin test
   - (*c*) Sedimentation rate determination
   - (*d*) Local skin and lymph node biopsy
   - (*e*) Bone marrow studies

B. Evaluation of Tuberculin Skin Test in Uveitis.—In all cases the PPD tuberculin skin test was done in first and second strengths for careful evaluation. Provided all other studies were negative, it was felt that a strongly positive skin test could be considered of diagnostic value in deciding whether or not antituberculous therapy should be used.

From these findings it is apparent that our most effective therapy of tuberculosis is achieved by the combined use of isoniazid plus streptomycin and paraaminosalicylic acid. This may be due to one or all of three possible factors, i. e., a synergism resulting from combined therapy, or a specific therapeutic value of each of these drugs for certain tuberculous strains, or a specific ability of each of these agents to penetrate and destroy separate portions of the tuberculous organism.

C. Toxicity of Isoniazid in Humans.—In this group of patients treated with isoniazid there was no evidence of any objective or subjective disturbances which could be considered toxic in origin. Wherever hepatic or renal pathology was suspected, special laboratory tests were done before starting isoniazid therapy.

TABLE 1.—*Clinical Evaluation of Isoniazid in Ocular Tuberculosis*

	Total Cases (94)	Strength Tuberculin		Onset Clinical Improvement, Wk.	Improved		Unimproved		Previous Therapy	Recurrences Following Isoniazid	Average Length of Therapy
		1st	2d		No.	(%)	No.	(%)			
Posterior uveitis	28	21	17	5.8	26	(93)	2	(7)	7	1	3-4 mo.
Anterior uveitis	27	19	8	3.8	14	(52)	13	(48)	5	0	3-4 mo.
Peripheritis and hemorrhage	16	12	4	5.3	11	(69)	5	(31)	5	0	3-4 mo.
Sarcoid	4	0	4	3.4	2	(50)	2	(50)	2	2	3-4 mo.
Keratitis	3	1	2	4	1	(33)	2	(66.6)	2	0	3-4 mo.
Episcleritis	3	1	2	3.8	1	(33)	2	(66.6)	0	0	2 mo.
Vogt-Koyanagi syndrome	1	0	1	Nil	0		1		1	0	4 wk.
Harada's disease	1	0	1	Nil	0		1		1	0	2 wk.
Parinaud's oculoglandular syndrome	1	1	0	1	1	(100)	0		1	0	2 mo.

D. Drug Administration.—The total 24-hour dosage of isoniazid was determined on the basis of 3 to 5 mg. per kilogram of body weight. All patients received an average of 300 to 400 mg. per day (orally). This was divided into 100 mg. at four- to six-hour intervals. In anterior segment lesions, isoniazid ointment (200 mg. per gram) was also used topically at bedtime.

E. Analysis of Clinical Results.—In Table 1, the data on 94 clinical cases are presented.

In most of the cases no marked changes were noted in the first two to three weeks of therapy, after which improvement was fairly rapid in those cases which did respond.

Patients with posterior uveitis, with periphlebitis and hemorrhage, responded best to therapy (69% improved). The next best response was noted in patients with anterior uveitis (52% improved).

Evaluation of the drug in other lesions treated could not be considered significant in view of the insufficient number of cases.

All cases were kept on therapy for a minimum of four months in spite of apparent clinical cures within two months in many instances. This prolonged therapy was based on the experimental studies, which showed that pathologic activity could be present despite a lack of clinical activity.

Recurrences following therapy appeared in only three cases, two of which were sarcoid in origin.

F. Conclusions.—1. Isoniazid has definite value in the treatment of ocular tuberculosis in humans (56 apparent cures in 94 cases).

2. Isoniazid appears to be a nontoxic and easily administered drug.

3. Isoniazid is inexpensive and removes the necessity of frequent office visits or hospitalization.

4. Isoniazid therapy must be continued for two to four weeks before clinical improvement can be expected. Treatment must be continuous for a minimum of four months to obtain a clinical cure.

CLINICAL STUDIES IN OCULAR TUBERCULOSIS (1954-1955)

Diagnostic Survey.—During the past year routine diagnostic tests done on private patients and clinic patients with uveitis (Delaware Hospital eye clinic) have included the toxoplasmin skin test and dye test.[43] Of the 12 cases of granulomatous uveitis treated, 2 (16.6%) had positive skin and dye tests for toxoplasmosis.

Combined Therapy.—As reported in the literature ‖ of 1954 and 1955, isoniazid and streptomycin are being used more extensively together as the preferred therapy in tuberculosis. Their synergistic effect is apparently resulting in a smaller number of resistant cases.

Therapeutic Trial.—In the cases with tuberculin-positive skin tests in which all other tests were negative, combined therapy (isoniazid and streptomycin) was tried for a period of three weeks in order to help establish the diagnosis. Wherever the response was positive, therapy was continued for a minimum of four months. All these cases have received 300 to 400 mg. of isoniazid per day along with 0.5 to 1 gm. of streptomycin twice a week.[54]

Antituberculous Drugs Plus Cortisone.—Despite reports in the literature contraindicating the use of cortisone in any form of tuberculosis,¶ the drug is being tried in conjunction with antituberculous drugs, with promising results.# It appears that cortisone, hydrocortisone, and corticotropic hormones may inhibit the inflammatory reaction surrounding the tuberculous lesion, thus making it possible for the antituberculous drugs to attack the tuberculous organisms more rapidly and more effectively.

Clinical Cases (Table 2).—In the past year 10 cases of probable ocular tuberculosis have been treated. Three were cases of chorioretinitis treated with isoniazid and streptomycin alone. The other seven were

‖ References 46 to 50.

¶ References 40 and 41.

References 52 to 55.

TABLE 2.—*Comparison of Therapeutic Results in Clinical Uveitis with Antituberculous Drugs Alone and with Antituberculous Drugs Plus Cortisone*

Condition	No. of Cases	Results		
		Excellent	Good	Fair
Chorioretinitis (isoniazid and streptomycin)	3	..	2	1
Iridocyclitis (combined drugs plus cortisone)	1	..	1	..
Chorioretinitis (combined drugs plus cortisone)	7	4	2	1
Total	10	4	4	2

cases of chorioretinitis[20] and iridocyclitis,* and all were treated with both antituberculous drugs and cortisone (orally).

Results obtained in the three cases treated by combined antituberculous drugs alone were fair to good. Beginning improvement usually was noted in the third week of therapy. On the contrary, treatment of cases with the addition of cortisone generally resulted in good to excellent response, improvement being noted within 7 to 10 days. Therapy was continued for the usual period of four months, although cortisone was gradually eliminated after apparent disappearance of clinical activity.

Results in these cases strongly suggest that the addition of cortisone inhibits the usual local tissue reaction which appears at the site of the tuberculous lesion, thus preventing the subsequent fibroblastic activity and resultant scar tissue formation. Chorioretinal atrophy and pigmentation have been markedly decreased. The clearing of vitreous opacities, as well as the decrease in chorioretinal inflammation proximal to the macula, papillomacular bundle, and disc, has resulted in excellent final visual acuity in these cases.

* E. R. Squibb & Sons, Institute for Medical Research, unpublished data from Research and Developmental Laboratories, 1952. References 1 to 15.

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Eccentric Fixation in Amblyopia Ex Anopsia

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Eccentric fixation is found in some cases of strabismus with deep amblyopia. When present, monocular fixation of the amblyopic eye does not occur along the foveal visual axis but is eccentric to it in a convergent, divergent, or vertical position, depending on the type of squint. In the cases discussed here, the eccentric area of fixation was at the angle of squint and so fixed that no movement of the eyes occurred with the cover test, even though a large squint was present.

According to Duke-Elder,[1] these findings mean that an eccentric point on the retina is chosen to take up fixation. They have been called cases of "false macula," or "functional macula," or "paracentral fixation." A perusal of the modern literature on the subject * leaves one with the impression that the amblyopia in these cases cannot be improved with occlusion of the good eye, and that occlusion of the good eye may be contraindicated, since it could stabilize the eccentric area and make it more fixed.

This paper will deal with a study of 98 cases of eccentric fixation examined and treated under my supervision during the past seven years at the Motility Clinic of the Illinois Eye and Ear Infirmary. Some problems of, and our methods for, carrying out proper occlusion therapy will be discussed. Our results of occlusion in the treatment of eccentric fixation will be tabulated according to Chavasse's theory of amblyopia. Chavasse's theory will be reexamined in the light of our results.

After seeing many squint cases, one gets the impression that amblyopia is not as common in exotropia as in esotropia. When the types of squint were tabulated, we found that the frequency of eccentric fixation was the same in esotropes as in exotropes, as compared with the over-all frequency found by Chavasse † in his large series of cases, i. e., about 10 cases of esotropia to 1 of exotropia (Table 1).

It was important to know the severity of the amblyopia in eccentric fixation. As can be seen in Table 2, all of the cases who were old enough to have visions taken had vision of less than 20/200, and in about 70% of the cases it was 5/200 or less. After occlusion therapy, it was found that all cases had centric fixation when the vision was brought up to 20/200. In one case centric fixation occurred with 15/200 vision.

Since almost none of the cases were of paralytic squint, it was of interest to see whether any of the factors that made one of the eyes amblyopic could be determined. It was found that the eccentrically fixing, amblyopic eye had the greater refractive error in about 60% of the cases, as compared with 18% for the fixing eye (Table 3). Eccentric fixation was found to be twice as frequent in the left eye as in the right (Table 1). Since most persons are right-eye-dominant, it is possible that ocular dominance could play the decisive role when all other factors were equal in the two eyes.

In this series of 98 cases, 58 had occlusion consisting of covering the good eye with an adhesive-plaster patch constantly, day and night, for at least six months when necessary. Our results are based on these 58 cases. Some patients improved in a few weeks;

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* References 2 to 4. Swan, K. C.: Sensory Physiology of Binocular Vision, in Allen,[5] p. 112. References 6 to 8.

† Worth,[9] p. 313.

Table 1.—*Data on Ninety-Eight Cases of Eccentric Fixation*

Right eye affected	32
Left eye affected	66
Exotropia	10
Esotropia	88
No. with occlusion	58

others, in a month or two; others did not show improvement. Six months was considered the minimum period for occlusion in the group that showed no improvement. As long as some improvement was evident, complete occlusion was maintained for as long as one to one and one-half years. The results obtained from complete occlusion depended a great deal on the age of the child when first seen and the attitude of the parents.

It was in children of preschool age that the best results could be obtained with occlusion therapy. These children, when the vision improved to 20/200, apparently had no trouble with their regular daily activities, for this amount of vision was useful to them. In working with these young amblyopes, the cooperation of the parents was found to be of the greatest importance. Unless we were able to make the parents understand what we were doing, cooperation was poor and occlusion unsuccessful. We were able to tell them that their child would have trouble for a week, or possibly less. After a week the patch would be worn with no complaint. Our being able to give a definite time limit was of great help and encouraged the harassed parents to persevere. The parents were also told about the complaints of the older children with amblyopia, who say, "It is my mother's fault that I cannot see in my poor eye. She did not insist I wear a patch when I was younger and did not understand its importance."

Table 2.—*Initial Visual Acuities in Ninety-Eight Cases of Eccentric Fixation*

Light perception and projection	1
Counting fingers (1 ft.)	12
1/200	12
2/200	8
3/200	12
4/200	6
5/200	13
6/200	2
8/200	1
10/200	7
12/200	1
15/200	1
Too young for accurate visual tests	22

In one case a child simply refused to wear the patch and the mother was at her wit's end. She asked whether there was anything that could be done to help her. The child was hospitalized for a week and had a nurse in constant attendance to see that the patch was not removed. Sedation was given when necessary. The result was excellent.

Before any child is given occlusion, the parents are warned that the eye under the patch may lose vision. They are told, however, about the following rule, which we have found to apply rather consistently. As the vision decreases in the occluded eye, the vision will increase in the open eye. With this rule in mind the parents are not disturbed by the profound loss of vision in the previously good eye. I have never seen a case in which the vision of the eye under the patch decreased without the vision improving in the open eye.

Table 3.—*Refractive Error in Ninety-Eight Cases of Eccentric Fixation*

Greater in fixing eye	15
Same in each eye	18
Less in fixing eye	50
Unknown	15

There are certain patients who are very sensitive to occlusion and lose vision in the eye behind the patch very quickly. The following case illustrates this.

Case 1.—R. W., aged 3½ years, came to the Infirmary on Jan. 20, 1949, with a history of crossing of the left eye since birth. With atropine cycloplegia, refraction was as follows:

O. D.: +3.25 sph ⌒ +1.00 cyl, ax 80 = 20/40
O. S.: +4.25 sph ⌒ +1.00 cyl, ax 90 = 5/200 eccentric fixation

There was 20 degrees of left esotropia for distance and near with and without glasses. Fixation in the left eye was eccentric at 20 degrees of convergence (Fig. 1*A*, *B*). With the cover test there was no movement. Complete occlusion of the right eye was instituted, and, since the child lived out of town, he was instructed to return in one month. Examination after one month of complete occlusion of the right eye revealed 20 degrees of right esotro-

pia with and without glasses for distance and near (Fig. 1*C*, *D*). Fixation was centric in the left eye, and vision had improved to 20/30. Now there was eccentric fixation of the right eye at 20 degrees of convergence and vision had dropped to 5/200. Again, no movement with the cover test was present. The parents and the doctor became worried when the child could not see out of his previously good eye. The parents were so concerned that I am sure they would have gone to another ophthalmologist if the child had not been a clinic patient. Complete occlusion of the left eye was instituted, and the parents were requested to bring the child back in one week. After a week, the original squint was again present and vision was 20/30 in the right eye and 5/200 in the left eye, with eccentric fixation. At this point, not knowing what else to do, we ordered that the eye that was seen to be straight upon arising in the morning be occluded for one-half day. For the rest of the day both eyes were to be left open. After one year, on March 29, 1950, examination revealed 5 degrees of alternating esotropia; vision was 20/30 O. D. and 20/50 O. S. (Fig. 1*E*, *F*).

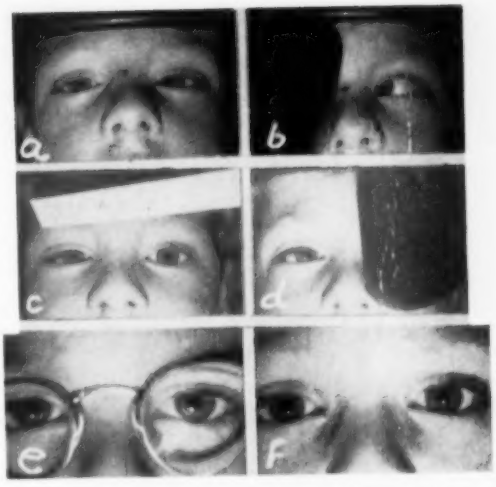

Fig. 1.—*A* and *B*, taken before patching. *A*, 20 degrees of left esotropia without glasses (same with glasses). Vision in the right eye is 20/30. *B*, eccentric fixation of the left eye at 20 degrees clinically. Photograph shows 50 degrees of esotropia. Vision in the left eye is 5/200.

C and *D*, taken after complete occlusion of the right eye for one month. *C*, right esotropia of 20 degrees without glasses (same with glasses). Vision in the left eye is 20/50. *D*, eccentric fixation of the right eye at 20 degrees of esotropia. Vision in the right eye is 5/200.

E and *F*, taken after one year of alternate occlusion and constant wearing of glasses. *E*, 5 degrees of right esotropia with glasses for distance and near. Vision in the left eye is 20/50. Fixation is centric. *F*, 5 degrees of left esotropia without glasses for distance and near. Vision in the right eye 20/30. Fixation is centric.

This case of congenital squint belonged to a group which might be designated as having alternating amblyopia. In these cases either the occluded or the squinting eye may develop marked amblyopia and eccentric fixation, depending on which is used. It seems that in these cases the retina of the eye not being used can lose vision and fixation at the least provocation, and can just as easily regain them. This might be the type of congenital or early squint seen at the age of 8, 9, or 12 years, in which normal vision returns after only a relatively short period of occlusion.

In older children, those above the age of 7 years, constant occlusion of the good eye has been a real problem and has been well expressed by the statement of nearly every parent, to wit: "But, doctor, he cannot see to do his school work!" The improvement in vision has been slow, with only a few exceptions, and the patience of children is very limited. They may keep the patch on conscientiously for a few weeks; but, if the vision has not improved to the point where it becomes useful for their purposes, they begin to peek. It seems as though adhesive just refuses to stick to their noses any longer. It is unbelievable how well a child can see through a small area where the patch is loose.

We have tried to get around the problem of school work by having patients over 8 years of age start complete occlusion when school is out. This has worked in very few cases. To say that the results of occlusion therapy are poor in older children is not completely correct, for, actually, complete occlusion therapy may not have been carried out. A child may wear a patch for six months or a year, but if peeking takes place we cannot call it adequate occlusion. Constant supervision is essential to see that occlusion is maintained. I believe occlusion should be tried in all cases. In a few of our cases the vision came back with extraordinary rapidity. In one 12-year-old child vision improved from 2/200 to 20/50 in one week.

The following case shows the return of vision and improvement in the squint at the age of 9 years, following patching.

Fig. 2.—*A* and *B*, before occlusion for amblyopia of the left eye. *A*, 20 degrees of left esotropia for distance and near without glasses (same with glasses). Vision in the right eye is 20/20. *B*, eccentric fixation of the left eye at 20 degrees of convergence. Vision in the left eye is 4/200.

C and *D*, after occlusion therapy had been carried out. *C*, eyes straight with glasses for distance and near. *D*, eyes straight without glasses for distance and near. *E*, centric fixation of the left eye. Vision 20/25.

Case 2.—V. G., aged 9 years, came to the Infirmary on Feb. 23, 1949, with a history of crossing of the left eye since 4 years of age. With atropine cycloplegia, refraction was as follows:

O. D.: +3.00 sph ⁻ +1.00 cyl, ax 80 = 20/30
O. S.: +5.00 sph ⁻ +1.50 cyl, ax 90 = 4/200

There were 20 degrees of left esotropia with and without glasses for distance and near (Fig. 2*A*). Eccentric fixation of the left eye was present at 20 degrees of convergence, and no movement with the cover test was found (Fig. 2*B*).

Complete occlusion of the right eye was ordered, even though the child was 9 years of age. After one week of complete occlusion, vision in the left eye had improved from 4/200 to 13/200. After two months of occlusion, vision in the left eye was 20/200 and fixation was centric. Occlusion for seven more months resulted in the left eye becoming dominant. Vision was 20/40 in the right eye and 20/25 in the left eye with correction. The esotropia was much improved (Fig. 2*C*, *D*, *E*). An occluder, to be placed over the lens of the straight eye for a few hours each morning, was ordered.

Cases of perfect occlusion are those of amblyopia ex anopsia in which vision in the good eye has been lost through disease or accident. One such case in my practice impressed me greatly with the fortuitous return of vision. A woman, aged 75, came to my office complaining of loss of vision in the right eye of one day's duration. Examination revealed that vision in the right eye had been reduced to 3/200 because of a venous thrombosis. The left eye had turned out since early childhood, and examination showed an exotropia of 25 degrees, vision of 1/200, and a normal fundus except for a few vascular changes. After six months, vision in the left eye improved from 1/200 to 20/50 and she could read newsprint.

Chavasse‡ promulgated the following theory of amblyopia ex anopsia, which has been widely accepted in the past. Briefly, he divided it into two components: 1. The "amblyopia of arrest," or the arrest of further development of vision, starting at the time of onset of the squint. Such vision as is present at this time is a completely conditioned reflex, especially after the age of 6 years, and therefore is easily regained on later treatment by occlusion. However, according to this theory, later treatment of amblyopia by occlusion cannot be expected to improve vision significantly beyond that present when the squint began; e. g., at birth less than 6/728, at 6 months 6/200, at 1 year 20/200, at 4 years 20/20, and at 6 years a fixed, or unconditional, reflex. 2. The "amblyopia of extinction." This represents the loss of vision which has already been developed as an unfixed, conditioned reflex and is related to the duration of the squint. Such loss of vision can be recovered more easily with occlusion therapy. From these considerations, the following questions would be of prognostic importance: How old was the patient when the squint was first noticed, and how old is the patient now?

We have tabulated the results of occlusion therapy in our series with Chavasse's ideas in mind. The age of onset of the squint and the age when occlusion was started have been recorded (Tables 4 and 5).

The results after adequate occlusion have been very reassuring and do not confirm the gloomy outlook on occlusion therapy for eccentric fixation recorded in most of the

‡ Worth,[8] p. 349.

TABLE 4.—*Vision After Occlusion of the Good Eye Compared with Age at Onset of Squint in Fifty-Eight Cases of Eccentric Fixation*

Age at Onset of Squint	Total Cases	Equal Vision	20/50	20/70	20/100	20/150	20/200	15/200	No Improvement
Birth to 6 mo.	20	15	..	..	3	1	1	..	..
7 mo.-2 yr.	21	16	1	1	1	..	..	1	1
2½-4 yr.	9	7	..	2	..	..	..	..	..
4½ yr. and over	3	2	..	..	1	..	..	..	..
Unknown	5	4	..	..	..	..	1	..	..

modern literature. They did confirm the findings of Miss Yoxell,[10] who reported the results of a series of 14 cases of eccentric fixation treated with occlusion. In her series, four cases took 6 months to obtain equal vision; six cases took from 6 to 28 months; three cases were still under treatment and improving, and one case failed to improve. In the cases that improved the ages varied from 3½ to 11½ years.

The most significant finding was that all cases aged 4 or less who had eccentric fixation obtained equal vision in the two eyes (Table 5). The final vision was usually 20/30 to 20/20. These excellent visual results were surprisingly different from those obtained by Chavasse.§ He was convinced that vision which had been arrested and had never developed as a conditioned reflex could not be improved later by occlusion; so he did not patch the eye in a child 5 years of age who had eccentric fixation with 30 degrees of esotropia. He operated immediately and reduced the squint to 10 degrees, without improvement in vision.‖

Our results do not confirm Chavasse's theory. However, in defense of this theory, it should be noted that in some cases it may be erroneous to date the onset of the development of the amblyopia at the time of the onset of the squint. It is well known,¶ that certain cases of originally alternating squint later become monocular and at this point begin to develop amblyopia. It is possible that certain cases are very sensitive to disuse of the eyes and can develop a true amblyopia ex anopsia when one eye becomes dominant, as in the case of alternating amblyopia discussed above. Occlusion therapy in these cases can be expected to bring back normal vision.

SUMMARY

In a series of 98 cases of strabismus with eccentric fixation, the vision in the amblyopic eye was always less than 20/200, and usually less than 8/200.

§ Worth,[9] p. 114

‖ Worth,[9] p. 628.

¶ Guibor,[11] Allen,[3] p. 346.

TABLE 5.—*Vision After Occlusion of Good Eye Compared with Age at Which Occlusion Was Started in Fifty-Eight Cases of Eccentric Fixation*

Age Occlusion was Started, Yr.	Equal Vision	20/50	20/70	20/100	20/150	20/200	15/200	No Improvement
2 (11 cases)	11	..	..	..	..	..	..	..
3 (6 cases)	6	..	..	..	..	..	..	..
4 (4 cases)	4	..	..	..	..	..	..	..
5 (12 cases)	8	..	1	..	..	2	..	1
6 (8 cases)	8	..	..	..	..	..	..	..
7 (1 case)	1	..	..	..	..	..	..	..
8 (2 cases)	1	..	..	1	..	..	..	..
9 (4 cases)	2	..	..	1	..	..	1	..
10 (5 cases)	1	..	2	1	1	..	..	..
11 (2 cases)	..	1	..	1	..	..	..	..
12 (3 cases)	2	..	..	1	..	..	..	..

The results of adequate occlusion therapy in 58 of these cases have been very encouraging. If occlusion was started before the age of 4 years, all cases obtained normal vision, and in many cases normal vision was obtained even up to the age of 12 years.

The age when occlusion was started was of greater importance than the age of onset of the squint. The older children were usually less willing to forego useful vision for a sufficient period to make proper occlusion effective.

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Reparation of the Fetal Eye Following Radiation Insult

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Radiation insult is immediate, but the cytological evidence for this insult may not follow for hours or days, depending, in part at least, upon the activity of the particular tissue under study. Histological and cytological analyses of exposed tissues days after exposure have not revealed the immediate disruptive and the subsequent reparative processes that occur. This study of the very early, and consequently radiosensitive, embryonic eye is made to bring out the sequence of responses to graded exposures of x-radiation. It reveals the remarkable powers of repair present in the embryo.

MATERIALS AND METHOD

CF, female mice were time-mated with males of the same strain and 12.5 days later were exposed to whole-body x-radiations. Irradiation was achieved by a Quandrocondex constant-potential therapy machine run at 210 kvp and 15 ma., and the rays were selectively hardened by filtration with 0.28 mm. Cu and 0.50 mm. Al. The distance to the center of the body (i.e., the gravid uterus) was 50 cm., and the output of the machine was 96.6 r/min. in air at that position. Pregnant mice were placed within a plastic cage measuring 14.5 cm. in diameter and 4 cm. in depth and were exposed to doses of 50, 150, 250, and 300 r.

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From the Radiation Research Laboratory, Columbia University.

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Animals were killed at intervals of 4, 24, and 72 hours after irradiation, and the uterine contents were fixed for study. The lowermost fetuses in each of the uterine horns were chosen for cytological examination, since they are presumed to be the furthest developed and more uniform. This method was adopted because there is considerable developmental difference among the fetuses in any uterus, due in part to the position (which might affect nutrition and respiration) and to the actual time of fertilization and implantation. Thus, by killing whole litters in utero but selecting the most advanced embryos, there was maximum consistency in the staging.

The pregnant mice were etherized and opened, and the uteri were slit open from the vagina to the infundibulum. The fetuses were removed intact and in the order in which they occurred, from the lowermost position upward in each uterine horn. All were fixed in Bouin's fluid, following severance of the head from the body by a clean cut with a razor blade. Fixation was achieved, with mild shaking, to insure complete penetration, for a period of at least 24 hours. The heads were dehydrated and cleared in xylene. They were sectioned transversely and serially from the anterior end, at a uniform thickness of 10μ. They were all stained with Delafield's hematoxylin without counterstain.

EXPERIMENTAL OBSERVATIONS

Pregnant mice x-irradiated on gestation day 12.5 all delivered their litters at the proper time provided the dose was not above 300 r. The fetuses exposed to 300 r died shortly after birth, but those exposed to 250 r lived until they were killed, at 6 weeks of age. The latter mice were slightly stunted and highly irritable, and the eyes appeared to be microphthalmic (Plate V, Figs. 27, 28). Thus, 250 r was established as the maximum tolerance dose for the 12.5-day fetus if survival for 30 days after parturition was the

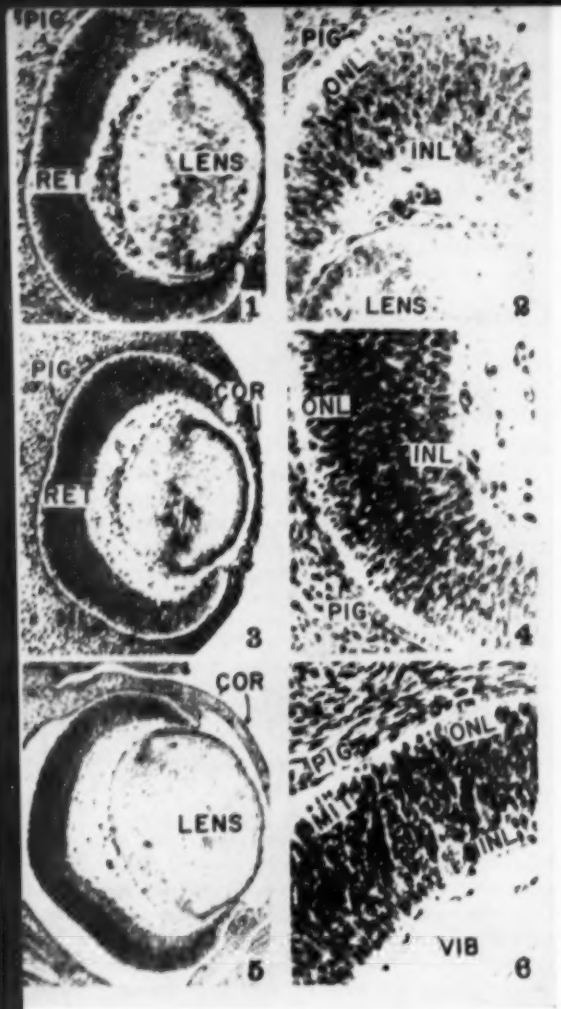

Plate I.—Mouse fetus exposed at 12.5 days' gestation to 50 r of x-rays.

Figs. 1 and 2: Eye at four hours after exposure, quite normal as compared with controls. Note mitoses, particularly in outer neuroblastic layer of embryonic retina. Few desquamated cells in vitreous body between retina and lens.

Figs. 3 and 4: Eye at 24 hours after exposure. Note abundant mitoses in outer neuroblastic layer. Desquamated cells in vitreous body disappearing.

Figs. 5 and 6: Eye at 72 hours after exposure, appearing quite normal and with abundant mitoses in area of presumptive rods and cones.

Summary: No radiation effect of 50 r aside from a few cells desquamated into vitreous body and cleaned up by 72 hours.

In this Plate, and in the accompanying Plates, *CHR*, indicates chromosomes; *COR*, cornea; *INL*, inner neuroblastic layer; *LENS*, lens; *MIT* mitosis; *ONL*, outer neuroblastic layer; *OPN*, optic nerve; *PHA*, phagocyte; *PIG*, pigmented layer of eye; *PYC*, pyknotic nuclei; *RET*, retina, and *VIB*, vitreous body.

criterion. These mice at 6 weeks appeared to be sufficiently healthy to survive.

The cytological study of the developing eye was made at 4, 24, and 72 hours after x-irradiation at levels of 50, 150, 250, and 300 r. Those exposed to the lowest dose (50 r) showed only slight desquamation of cells into the vitreous body, without any obvious effect on developing retinal mitoses. The usual abundance of mitotic figures in the outer neurectoderm layer of the retina was observed (Figs. 1-6). This is the presumptive rod layer of nuclei, and consists at this time of neurectoderm in active differentiation into neuroblasts.

Exposure of the 12.5-day fetus to 150 r did not show appreciable damage by 4 hours (Fig. 7), but by 24 hours (Figs. 8, 9) both the inner and the outer zone of the differentiating neuroblastic retina were filled with scattered pyknotic nuclei. In the outer neurectoderm zone there appeared to be a few quite normal-looking mitotic figures. There was no evidence of cytological damage to the lens, the pigmented layer, or the presumptive cornea. By 72 hours there appeared a few phagocytes in the space between the retina and the pigmented layer (Fig. 10), but the embryonic retina appeared to be re-formed and had lost most of its damaged cells and nuclei (Fig. 11). There were definite mitoses in the outer (presumptive rod) layer. Thus, by 72 hours after irradiation with 150 r at 12.5 days the eye of the fetal mouse began to look again like that of the control (Fig. 12).

Exposure of the 12.5-day fetus to 250 r of x-rays resulted in maximum cytological damage by four hours after exposure (Figs. 13, 14). This suggests that as the dose is increased, more and more cells are damaged (the radiosensitive level of more and more cells is reached). The time interval for evidence of necrosis is therefore shortened. Many pyknotic nuclei and dead cells are sloughed off into the space between the developing retina and the pigmented layer, and a few into the vitreous body. Both the inner and the outer neuroblastic zone nuclei are involved in this radiation response, but the lens,

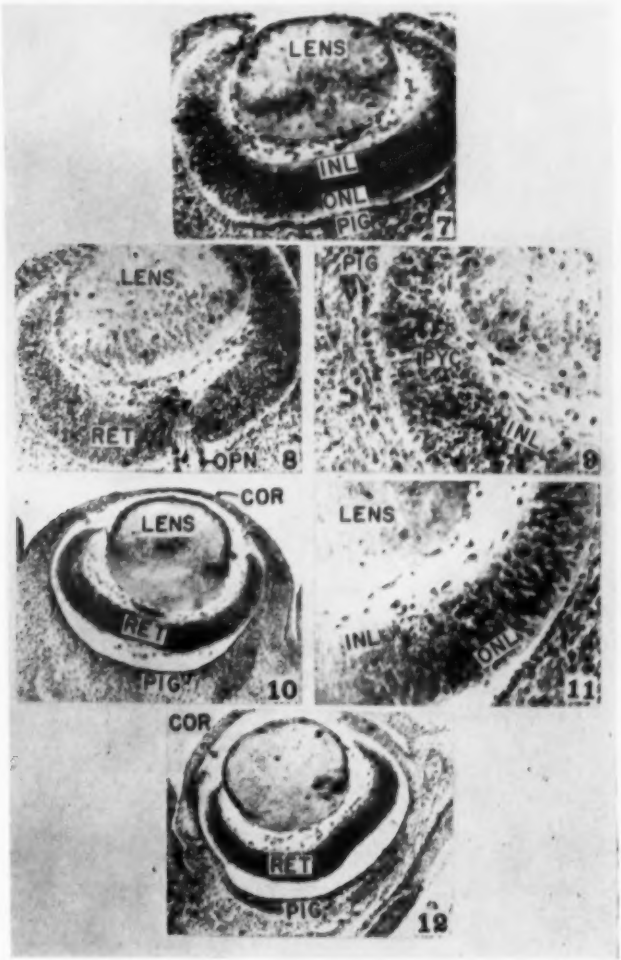

Plate II.—Mouse fetus exposed at 12.5 days to 150 r of x-rays.

Fig. 7: Eye at four hours after exposure, appearing quite normal with respect to retina but showing some cells desquamated into vitreous body. Few pyknotic nuclei in outer neuroblastic layer.

Figs. 8 and 9: Eye at 24 hours after exposure, showing abundant pyknotic nuclei in both inner and outer neuroblastic layers, and a few chromosome masses in attempted mitoses.

Figs. 10 and 11: Eye at 72 hours after exposure, showing some repair of retina but areas of persistent damage to nuclei in both inner and outer neuroblastic layers. More definite chromosome clusters in outer than in inner zone. Vitreous body relatively clean.

Fig. 12: Control, normal eye, at 12.5 days, showing intact retina, in which nuclei of inner and outer layers can be distinguished. Note absence of free cells in vitreous body or between retina and pigmented layer.

Summary: Radiation damage of 150 r maximum by 24 hours, with no evidence at 4 hours. At 72 hours considerable repair, with resumption of mitosis.

presumptive cornea, and pigmented layers appear to be unaffected.

By 24 hours the 12.5-day fetus exposed to 250 r shows active processes of repair. There are numerous phagocytes in the spaces both in front of and behind the retina, and these phagocytes can be seen ingesting the dead cells and nuclei (Figs. 15-17). Some phagocytes may also be seen within the retina itself (Figs. 15, 16). A single phagocyte was found

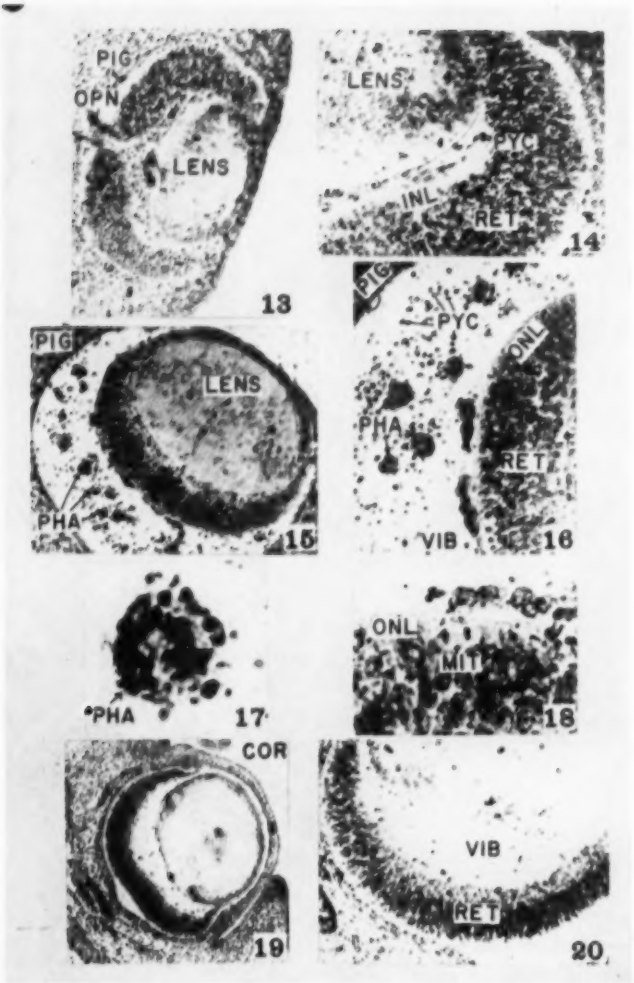

Plate III.—Mouse fetus exposed at 12.5 days to 250 r x-rays.

Figs. 13 and 14: Eye at four hours after exposure. Note widespread pyknosis in both inner and outer neuroblastic zones of retina, with cells desquamated into both vitreous body and space between retina and pigmented layer. Maximum damage.

Figs. 15 and 16: Eye at 24 hours after exposure. Note only scattered pyknosis throughout retina, but some evidence of repair. Numerous cells and pyknotic nuclei from retina desquamated into enlarged space between retina and pigmented layer and being ingested by active phagocytes. Toward the inner neuroblastic layer of the retina can be seen clumped chromatin masses (Fig. 16).

Fig. 17: Enlarged photograph of a single phagocyte after ingestion of some 12 or more radiation-killed cells.

Fig. 18: Enlarged view of anaphase in outer neuroblastic layer, exhibiting lingering chromosome.

Figs. 19 and 20: Eye at 72 hours after exposure, showing quite normal retina with evidences of mitoses in outer neuroblastic layer particularly. Desquamated cells all cleaned up by phagocytosis.

Summary: At this higher level of exposure (250 r) the eye shows maximum damage by 4 hours with active repair and phagocytosis by 24 hours, and quite normal-appearing retina by 72 hours.

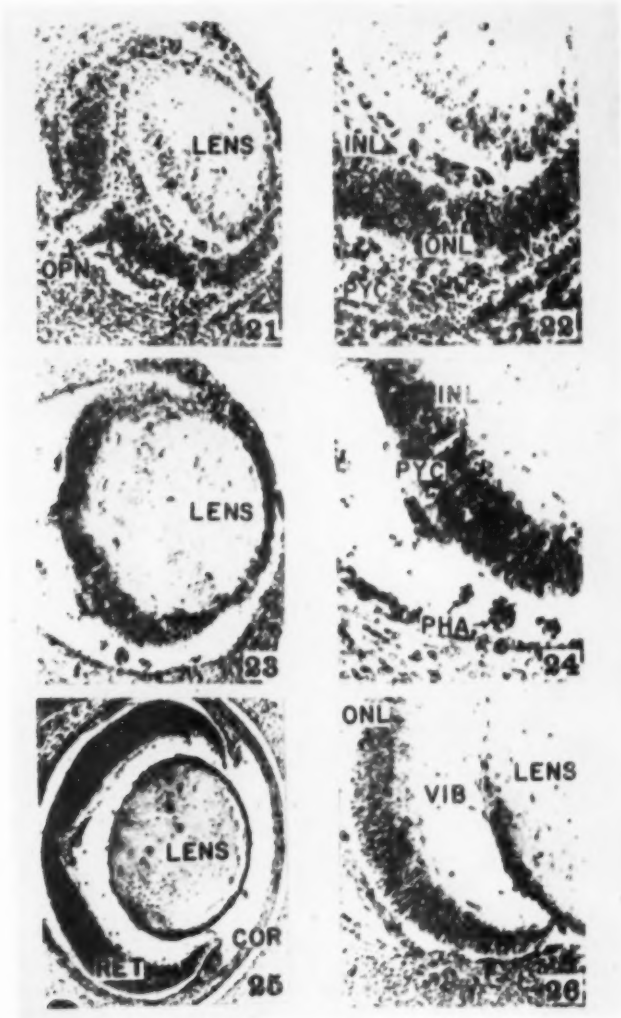

Plate IV.—Mouse fetus exposed at 12.5 days to 300 r x-rays.

Figs. 21 and 22: Eye four hours after exposure. Note widespread damage to retina but not to lens. Pyknosis and karyorrhexis in both inner and outer neuroblastic zones with partial obliteration of retina. Most damaged cells liberated into space between retina and pigmented layer; few in vitreous body.

Figs. 23 and 24: Active phagocytosis in space between retina and pigmented layer, artificially enlarged by prior aggregations of cells. Note also some phagocytosis within retina itself, also pyknotic nuclei, and clumped chromosome masses.

Figs. 25 and 26: Normal-appearing eye 72 hours after exposure. All pyknotic nuclei, karyorrhetic particles, and chromosome masses have been cleaned up by phagocytes. Note numerous mitoses in outer neuroblastic layer (presumptive rod layer).

Summary: With this highest level of exposure (300 r), the maximum dose tolerated by fetuses of this age, damage was maximum by 4 hours, phagocytosis achieving excellent cleaning up by 24 hours; and by 72 hours retina and entire eye appear to be quite normal, with resumption of mitoses.

to contain at least 12 dead cells or nuclei (Fig. 17). Mitosis continued but was abnormal in that the chromosomes were sticky, and there were bridges between the anaphase chromosomes (Fig. 18). Mitoses were most abundant in the outer neurectoderm zone.

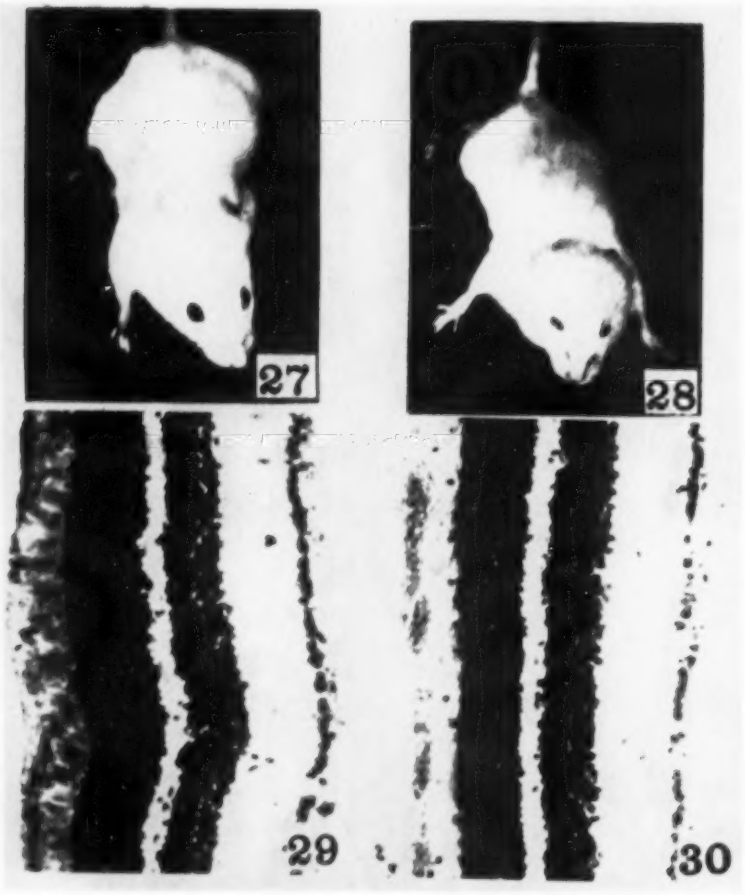

Plate V.—Fig. 27: Control mouse at 6 weeks of age. Note eyes and shape of head.

Fig. 28: Experimental mouse exposed in utero at 12.5 days to 250 r of x-rays, shown at 6 weeks of age. Note slightly reduced head and body and microphthalmia. Eye volume measured 50.6% that of control.

Fig. 29: Retina of control mouse at 6 weeks of age.

Fig. 30: Retina of experimental mouse exposed to 250 r at 12.5 days' gestation, shown at 6 weeks of age. From left to right, compare with control (Fig. 29) ill-defined rod layer, slightly reduced (thickness) of outer and inner nuclear layers, and interrupted ganglion cell layer of nuclei. These differences are attributable to radiation damage persistent since fetal life.

Paired figures are enlarged to the same degree.

In spite of this extreme cytological damage, the contour of the retina remained intact.

By 72 hours following 250 r to the 12.5-day fetus the eye appeared to be quite normal (Figs. 19, 20). The large accumulation of loose and dead cells and nuclei seen at 24 hours was cleaned up and removed, and the spaces on either side of the retina were again clear and clean (Fig. 20). Mitoses were evident, particularly in the outer neurectoderm, or rod zone, where there is usually active proliferation of cells. At this time the eyes appeared to have suffered little radiation damage. This is due to the activity of the phagocytes and the ability of the developing eye to reconstitute itself.

The highest level of radiation used was 300 r, to the 12.5-day fetus. The young mice

never survived this exposure very long after birth, but it was possible to get the reactions at 4, 24, and 72 hours after exposure. At four hours after irradiation the retina appeared cytologically to be damaged beyond repair (Figs. 21, 22). Roughly less than less than half the cells of the retina appeared undamaged, while the balance were fragmented and the nuclei pyknotic. The space between the retina and the pigmented layer was grossly enlarged by the accumulation of dead cells, derived from the retina. Taking these into consideration, one might estimate that upward of two-thirds of the retinal cells were radiation-affected under these conditions. No mitoses were seen. Such cytological damage was not evident in the lens, pigmented layer, or presumptive cornea.

By 24 hours following irradiation at 300 r of the 12.5-day fetus most of the loose and dead cells and nuclei had been cleaned up by very active phagocytosis (Figs. 23, 24) both in the spaces surrounding the retina and within the retina itself. There were clumped chromosomes within the retina and also phagocytes filled with dead-cell debris. While the thickness of the retina was slightly reduced, it was again taking on some semblance of a normal retina. By 72 hours there was little, if any, retinal damage (Fig. 25, 26), and numerous mitotic figures again appeared in the outer neurectodermal zone (presumptive rod layer).

Some litters, irradiated at these various levels on gestation day 12.5, were allowed to survive and were killed at 6 weeks of age in order to determine whether there might be any residual or persistent damage to the eyes, even though the eyes 72 hours after exposure appeared to be fully re-formed and normal. A mouse thus exposed in utero and photographed at 6 weeks is shown in Figure 28. One may note the general reduction in body size as compared with that of the unirradiated control (Fig. 27), the peculiarly shaped head, and microphthalmia. When the eyes are dissected out and the diameters taken, it is clear that with increasing exposure in utero there is decreasing size (volume) of the eye.

*Measurement of Mouse Eyes at 6 Weeks of Age**

	Average Diameter, Mm.	Relative Volumes, %
Controls	3.355	100
150 r at 12.5 days	2.970	69.6
250 r at 12.5 days	2.670	50.6

* A minimum of eight diameters of fixed eyes was taken for each average.

Thus, there is progressive reduction in the diameter (and volume) of the eyeball, depending upon the level of exposure of the fetus at 12.5 gestation days. This over-all reduction in size of the eye is not reflected in a parallel or comparable reduction in the retinal elements (Figs. 29, 30). Figure 30 shows the retina at six weeks following exposure to the highest level (250 r) at 12.5 gestation days. There is some disruption of the rod layer, some thinning of both the outer and the inner nuclear layer, and a definite interruption of the ganglion cell layer of nuclei. It would be difficult to determine the degree to which these radiation-induced changes affect the visual acuity of the mouse. However, when one reflects on the condition of this retina at 4 or 24 hours after the radiation insult, it is quite obvious that a major repair of a relatively permanent nature has been achieved.

COMMENT

It is generally considered to be true that the earlier the stage in development the more sensitive is an organism or its parts to radiation insult. This is not strictly true, however, as the newborn mouse appears to be more radioresistant than it would be some four weeks later (Abrams[1]). With specific regard to the retina, Lorenz and Dunn[4] and Vogel[5] exposed the heads of newborn mice to 1000 r of x-rays and found marked pathological changes in the retina within three to four hours. While the exposure was high, much higher than the 100% lethal dose for the animal, the result does indicate that there are in the retina even at birth many nerve elements which have not yet fully differentiated into neurones.

As one studies earlier (fetal) stages, it is apparent that the retina is a very radiosensitive organ at the time of its neural differen-

tiation, i. e., from about gestation day 10 until birth. The present study is concerned with the earlier fetal eye (at 12.5 days' gestation), at a time when the presumptive retina consists of no mature neurones but is made up of abundant neurectoderm cells which are in the process both of proliferation (mitosis) and of differentiation into neuroblasts, in anticipation of the further differentiation into neurones. In the literature, the earliest suggestion of retinal damage in the embryo by x-rays was probably that in the salamander larva (Rugh,[5] 1949), but those studies were terminated within hours of exposure at a very high level. Similar effects on the newborn rat eye by neutrons and gamma rays from radium were previously shown by Tansley and associates[10] and Spear and Tansley.[9] Russell,* Wilson and Karr,[12] Wilson and associates,[13] and Hicks[2] derived schedules of embryonic development in the mouse and the rat, and those schedules were based upon the malformations produced by x-irradiation of the fetus at various stages of development. All emphasized microphthalmia, anophthalmia, and other eye aberrations as inevitable sequelae to certain levels of exposure at certain fetal ages. Thus, the radiosensitivity of the developing eye has been well established.

Recently, however, Hicks,[3] while studying the neural differentiation of the mammal, established the fact that "complete or nearly complete repair can occur in many zones." The current study substantiate the thesis of Hicks that the fetal eye, radiosensitive as it is to x-ray insult at 12.5 days' gestation, can nevertheless repair and reconstitute the retina so that it becomes functional in the adult mouse. That it is functional is proved by the avoiding behavior of the living mouse.

By subdividing the time intervals from four hours to six days, and by using a single stage of development (i. e., 12.5 days), it has been possible to reveal both the rapidity of radionecrosis and the rate of repair in the retina. By four hours after exposure generally there appears some evidence of radiation damage, if there is to be any damage at all. This is not true at the 150 r level, but is true at all higher levels. A dose of 50 r appears to be below the threshold for necrotic changes, but the possibility of functional abnormalities occurring at maturity or cataract development is not precluded. Such possibilities are under study. But at 150 r there is extensive necrosis seen at 24 hours, and this is cleared up by 72 hours. Thus, this dose level subjects the most radiosensitive cells to damage and the response is delayed. However, as the exposure is increased to 250 or 300 r, the same type of necrosis occurs at an earlier stage, i. e., at 4 hours, while at 24 hours there is evidence of active phagocytosis. Undoubtedly, more cells are damaged at the higher level, and more cells exhibit damage at an earlier stage after irradiation. The presumptive retina at four hours after irradiation with either 250 or 300 r appears to be irreparably damaged, the degree of pyknosis and karyorrhexis being so extensive. However, with the greater radionecrosis there appears to be greater phagocytosis, and the result is that by 72 hours after irradiation, all retinae, at any dose level used, are "cleaned up" and appear to be wholly reconstituted. Not only are the phagocytes seen in the spaces surrounding the retina, but some are seen invading the presumptive retina itself. These arise, undoubtedly, from the small capillaries of the eye. The efficiency and rapidity of action of these phagocytes are astounding, for they not only ingest all of the cellular debris but thereafter disappear from the ocular field and cannot be accounted for.

Fetal mice exposed on day 12.5 to 300 r did not survive for many days after delivery, but those that were exposed to 250 r lived quite normally and were carried along for six weeks, at which time they were killed for the study of adult eyes. These mice were not, however, entirely normal. They were stunted, had distorted heads, and were microphthalmic (Fig. 28). Their vision must be reasonably good, as is proved by their ability to escape capture. However, when their eyes were removed and measured, it was quite

* References 6 and 7.

obvious that the greater the radiation insult during fetal life, the smaller were the eyes of the adult. In fact, a dose of 250 r resulted in a 50% reduction in eye volume, although the cytological structure of the retina did not reflect the same degree of reduction.

SUMMARY AND CONCLUSIONS

Fetal CF_1 mice were exposed on gestation day 12.5 to x-rays in doses ranging from 50 to 300 r, and the eyes were examined at 4, 24, and 72 hours and at 6 days and 6 weeks thereafter to determine the cytological changes caused by the irradiation.

An exposure of 50 r had no discernible effect.

An exposure of 150 r caused extensive retinal radionecrosis by 24 hours after irradiation, but this was cleaned up at 72 hours.

An exposure of 250 or 300 r caused about half of the presumptive retinal cells to break down or become pyknotic by four hours after irradiation. The damage was so extensive that cells continued to break down as they attempted mitosis. The active phagocytes were unable to clean up the debris until about 72 hours after exposure.

The greater the radiation insult, the earlier the evidence of cytological radionecrosis.

All x-irradiated fetal eyes exposed at 12.5 days to any level of radiation used appeared to be fully "repaired," or the retina was "reconstituted," by 72 hours after exposure.

While all exposed retinae were "reconstituted," they gave evidence of persistent damage in the form of microphthalmia. Fetal eyes exposed to 250 r had approximately 50% the volume of control eyes at the adult stage of 6 weeks. The retina was not proportionately reduced in thickness.

While the early fetal eye is extremely radiosensitive, it exhibits remarkable powers of repair and reconstitution. Whether the eye is functionally altered will have to be determined.

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Carbohydrate Metabolism of Lens

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It has been generally assumed that the glucose metabolism in the lens is similar to that which predominates in other tissues. In most mammalian tissues glucose is catabolized first anaerobically to lactic acid by a process known as the glycolytic pathway and thence aerobically to carbon dioxide by a process known as the citric acid cycle. But the peculiar avascularity of the lens and its low oxygen consumption do not allow one to make any a priori assumptions as to the utilization of glucose by the lens. It is known that oxygen is essential for the maintenance of the viability of the lens,[1] but heretofore no study has been made of pathways in the lens other than the classical types just referred to.

The present paper reports a study of aerobic pathways of carbohydrate metabolism and a quantitative evaluation of their relative importance. It will be pointed out that an alternative pathway, the so-called direct oxidative cycle, or hexose monophosphate shunt, not only exists in the lens but appears to be the aerobic pathway of major importance. Furthermore, it will be shown that the requirements of this system may explain some of the peculiar biochemical characteristics of the lens.

For comparative purposes, a chart (Fig. 1) has been prepared showing glucose catabolism by way of the conventional glycolytic and citric acid pathways and by way of the direct oxidative cycle, or shunt, mechanism.

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METHODS

Many of the methods and materials used here were described in previous papers.* The isotopic glucoses, obtained from the National Bureau of Standards, were diluted with nonradioactive glucose and recrystallized from aqueous alcohol. The potassium 2-C^{14} pyruvate was made from 2-C^{14} pyruvamide,[4] purchased from Tracerlab. Specific activities of glucose and pyruvate were determined by the wet-combustion method of Van Slyke and Folch.† The specific activity of lactate was assayed by the method of Brin [7] after separation from glucose was effected by a method previously described.[3] All radioactivity assays were made with an end-window Geiger tube and corrected for background and self-absorption.

The experiments with isotopic substrates were incubated with intact lenses contained in an Erlenmeyer flask equipped with a side-arm and center well. Usually 8.0 ml. of the buffer was used in each reaction flask. When either the Krebs-Ringer bicarbonate buffer or aqueous humor was employed, the gas phase was 95% O_2 and 5% CO_2. Air was the gas phase for the phosphate buffer, which contained 0.04 M NaK phosphate buffer, pH 7.5; 0.08 M NaCl, and 0.005 M $MgSO_4$. After four hours of incubation at 37.5 C, 1.0 ml. of 1 N sulfuric acid was injected through the side-arm to release the CO_2. The CO_2 was collected by injecting 15% sodium hydroxide into the center well through a rubber port fitted in the stopper. Aliquots of the CO_2 recovered were analyzed for CO_2 content [8] and radioactivity.[3] The entire contents of the flask were then quantitatively transferred into a graduated 25 ml. tube. The lenses were homogenized, and the mixture was diluted to the 25 ml. mark. After centrifugation, aliquots were withdrawn to determine by standard methods the lactic acid [9] produced and the amount of glucose [10] or pyruvate [11] left after incubation. To determine the amount of glucose or pyruvate utilized, it was necessary to establish not only the amount of substrate added but also the amount contained in the lens itself.

* References 2 and 3.

† References 5 and 6.

For this purpose, to a series of flasks (at least 12) containing the same amount of substrate and buffer used in the incubation flask, the lenses were added, followed immediately by the addition of acid. The contents were transferred to a graduated 25 ml. tube, and the steps were taken, as described above, to obtain the measure of the substrate. The mean of the initial values, obtained in this manner, minus the mean of the values obtained after incubation was taken as the amount of substrate utilized.

RESULTS AND COMMENT

Citric Acid Cycle.—The pathway implicated in the aerobic phase of glucose metabolism in most tissues is the citric acid cycle. Since by this mechanism pyruvate is completely oxidized to CO_2, it seemed that an indication of the activity of this cycle might be gained by studying how effectively the lens would oxidize 2-C^{14} pyruvate to $C^{14}O_2$.‡

TABLE 1.—*Pyruvate Metabolism of Bovine Lens*

	Initial μM	Final μM
Pyruvate	181 ± 1.5	181 ± 1.8
Lactate	18.7 ± 0.5	19.5 ± 0.7
Pyruvate to:		
CO_2		0.3 ± 0.04
Lactate		10.7 ± 0.9

Incubation medium was composed of phosphate buffer, pH 7.5, containing two bovine lenses, and the specific activity of the pyruvate was 800 cpm/μM. The results are expressed as the mean plus or minus the standard error in μM/4 gm. wet weight/4 hr.

Therefore two bovine lenses were incubated with 2-C^{14} pyruvate, and the amount of radioactivity incorporated into carbon dioxide and lactic acid after four hours of incubation was determined. From the amount of radioactivity recovered, it was possible to calculate how much of the pyruvate was converted to these products. The results are shown in Table 1.

Within the precision of the colorimetric tests employed, it appears that lens was unable to utilize pyruvate to any appreciable extent. Furthermore, the amount of $C^{14}O_2$ recovered indicated that only 0.3 μM (micromole) of pyruvate was oxidized to CO_2. Pyruvate undoubtedly entered the lens, since 10.7 μM of the lactate recovered at the end of the incubation was radioactive. It seems the lens catalyzed the equilibration of the radioactive pyruvate with the nonisotopic lactate without a decrease or an increase in the amount of either component. These findings tend to indicate that the citric acid cycle is relatively inactive in lens.

Direct Oxidative Pathway.—We then explored the possibility of the presence of other aerobic pathways in lens and demonstrated that the utilization of glucose may proceed by way of the direct oxidative pathway. The relationship of this pathway to the glycolytic route is shown in Figure 1. It is possible to demonstrate (1) the two-step oxidation of glucose-6-phosphate resulting in the cleavage of the carbon-1 atom of the glucose moiety to CO_2 and in the formation of pentose-5-phosphate; (2) the conversion of pentose-5-phosphate to sedoheptulose phosphate, and (3) the resynthesis of hexose phosphate from the heptulose phosphate. The resynthesis of glucose-6-phosphate (G-6-P) § completes the metabolic cycle and provides another means by which glucose can be converted to CO_2. The participation of oxygen appears to be involved in the reoxidation of the TPNH (reduced TPN) formed in the oxidation of the hexose phosphate. Therefore this alternate route, like the citric acid cycle, is regarded as an aerobic pathway.

To demonstrate the presence of this cycle in lens, activities of the various enzymes were determined. In the two-step oxidation of G-6-P, two enzymes are involved, G-6-P and 6-PG dehydrogenases. Both of these dehydrogenases require the presence of TPN as their coenzyme. The activities of the enzymes can therefore be measured by following the reduction of added TPN in the presence of their respective substrates when

‡ In 2-C^{14} pyruvate, the radioactive carbon (C^{14}) is incorporated in the middle of this 3-carbon compound. The yield of $C^{14}O_2$ is then taken as an index of the complete oxidation of the pyruvate.

§ The following abbreviations will be used throughout the text: G-6-P, glucose-6-phosphate; 6-PG, 6-phosphogluconic acid; P-5-P, pentose-5-phosphate; R-5-P, ribose-5-phosphate; TPN, triphosphopyridine nucleotide; TPNH, reduced TPN; —P, phosphate; GSH, glutathione, GSSG, oxidized glutathione.

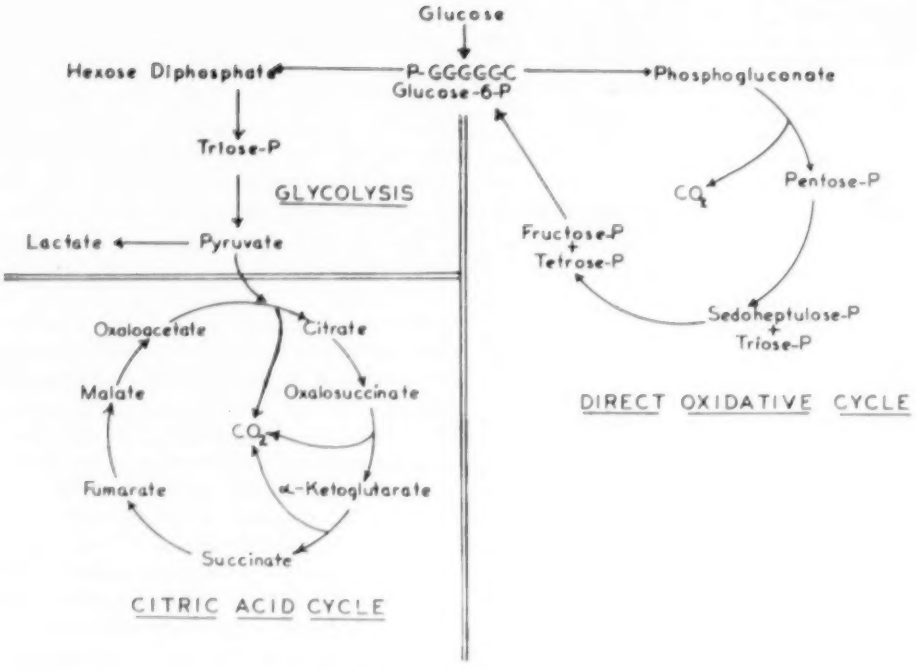

Fig. 1.—Pathways of glucose metabolism.

incubated with lens homogenate. The results are shown in Figure 2. According to the method of Glock and McLean,[12] the G-6-P dehydrogenase activity is the difference between the two curves. It appears that in lens these two dehydrogenases exhibit equal activities, indicating that they are present in about the same concentrations. The rabbit lens was shown to be about 1.5 times more active than the bovine lens. Preliminary experiments indicate that in bovine lens the homogenate of the anterior capsule and epithelium is about 10 times more active than that of the cortical fibers.

The enzymatic conversion of the pentose phosphate to hexose phosphate was next studied. The details of these reactions have recently been worked out in liver, spinach, and yeast by Horecker and associates.‖ A similar mechanism seems to occur in the corneal epithelium.[2] The results of the utilization of ribose-5-phosphate (R-5-P) when

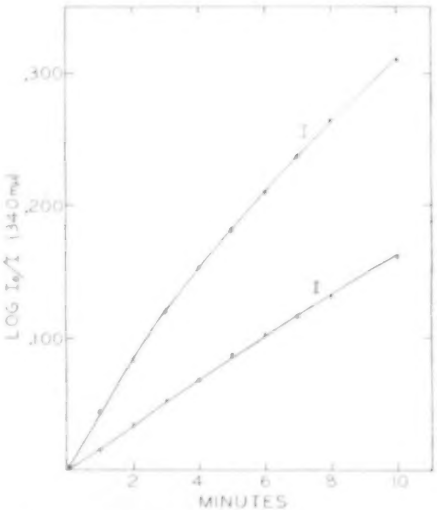

Fig. 2.—Dehydrogenases of the direct oxidative pathway. Cuvette *I* contained 5 μM of G-6-P and 6-PG; *II* contained 5 μM of 6-PG, and in each cuvette there was 0.2 μM of TPN and 0.05 M tris-(hydroxylmethyl)-amino methane buffer, pH 7.4, to make the total volume 3.0 ml. The reaction was run at 25 C, and absorption readings at 340 μM were made in a Beckman spectrophotometer.

‖ References 13 and 14.

incubated with lens homogenates is shown in Table 2.

From previous investigations [¶] it appears that two pentose phosphate molecules react to form sedoheptulose phosphate and triose phosphate, catalyzed by the enzyme transketolase. These intermediates then react further to form hexose phosphate. The stoichiometry of the reaction would indicate that the sum of the heptulose and hexose phosphates should equal one-half of the amount of R-5-P utilized. The results with lens homogenate seem to indicate that 10.3 μM of R-5-P was utilized and 4.8 μM of heptulose and hexose phosphates was formed. Analysis of the hexose phosphate recovered, by methods previously described,[2] revealed that it was a mixture of glucose and fructose phosphates. On the basis of the results obtained with lens homogenates, it appears that enzymes are present in sufficient quantities to suggest the possibility that glucose metabolism may proceed by the direct oxidative cycle.

[¶] References 2 and 13.

TABLE 2.—*Utilization of Ribose-5-Phosphate in Bovine Lens Homogenate*

	Micromoles
Ribose-5-phosphate utilized	10.3
Sedoheptulose phosphate formed	4.8
Hexose phosphate found	0.5

The reaction mixture contained 20 μM of R-5-P, dialyzed bovine lens homogenate (120 mg. wet weight), and 0.05 M phosphate buffer, pH 7.5, to make the total volume 3.0 ml. The reaction was incubated for two hours at 37.5 C and terminated with 2.0 ml. of 10% trichloroacetic acid.

Estimation of the Significance of the Direct Oxidative Pathway.—The demonstration of the enzymes necessary to operate the alternate route does not indicate how much of the glucose metabolism is directed through this pathway. Therefore an attempt was made

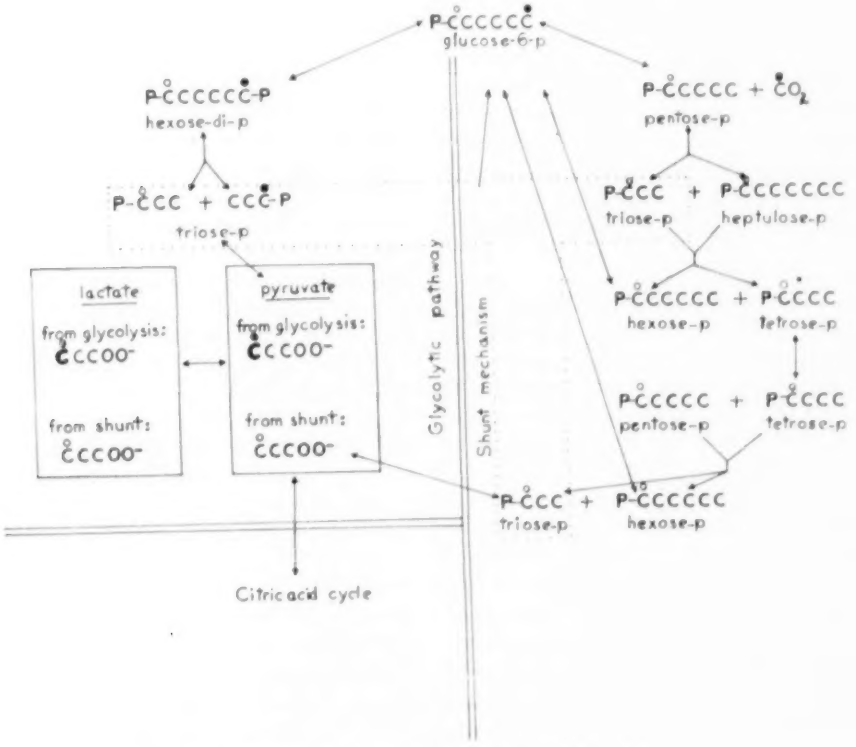

Fig. 3.—Metabolism of carbon atoms 1 and 6 of glucose.

to determine how active a role this pathway played in the over-all metabolism of the lens. As shown diagrammatically in Figure 3, the metabolic fate of the carbon-1 and carbon-6 atoms of glucose differs depending on how glucose is metabolized. If a tissue were to metabolize glucose via the glycolytic and citric acid pathways exclusively, the carbon atoms 1 and 6 of glucose become the methyl carbon of pyruvate, and subsequent oxidation by the citric acid cycle would result in C-1 and C-6 of glucose appearing as CO_2 simultaneously. If glucose were metabolized via the direct oxidative pathway, the C-1 atom of glucose would appear as CO_2 much earlier than C-6, since there is preferential cleavage of the C-1 of glucose. To subject this approach to experimentation, lens was incubated with either 1-C^{14} or 6-C^{14} glucose, and a comparison was made of the conversion of the isotopic carbon of glucose to $C^{14}O_2$. The results are shown in Table 3. The results can be expressed as a ratio of $C^{14}O_2$ recovered from $\frac{1\text{-}C^{14}\ \text{glucose}}{6\text{-}C^{14}\ \text{glucose}}$. In lens from different animals incubated in Krebs-Ringer buffer the ratio observed was about 40. If glucose had been metabolized via the glycolytic and citric acid pathways, a ratio of 1 would have been observed. It therefore appears that in lens there occurs a preferential oxidation of the C-1 of glucose to CO_2.

TABLE 3.—*Glucose Oxidation in Lens*

Tissue	Buffer	Total Cpm Recovered as $C^{14}O_2$ from 1-C^{14} Glucose	Total Cpm Recovered as $C^{14}O_2$ from 6-C^{14} Glucose	Ratio C-1/C-6
Cat lens	Krebs-Ringer	3080	84	43
Rabbit lens	Krebs-Ringer	4040	108	37
Bovine lens	Krebs-Ringer	2855	73	39
Bovine lens	Aqueous humor	3480	61	57
Bovine lens	Phosphate	2004	48	43

Incubation medium contained 0.020 M glucose, and the specific activity of 1-C^{14} and 6-C^{14} glucose was 920 cpm/μM. The values are given as the cpm/4 gm. of wet weight/4 hr.

With a few assumptions, an interpretation of the results in Table 3 can be made to contrast directly the activities of the citric acid cycle and the direct oxidative pathway. An assumption is made that all the radioactivity incorporated in the CO_2 from 6-C^{14} glucose resulted from the citric acid cycle. In bovine lens, the 73 cpm recovered in CO_2 from 6-C^{14} glucose divided by the specific activity of glucose, 920 cpm/μM, indicates that 0.08 μM of glucose was oxidized to CO_2 via the citric acid cycle. Since there are six carbon atoms in glucose, the amount of carbon dioxide produced via the citric acid cycle would be 6×0.08, or 0.48 μM. In estimating the amount of CO_2 from the shunt mechanism, it is assumed that in bovine lens only the first carbon of glucose is oxidized to CO_2 by this pathway. From the results it appears that carbon 1 from 2855/920, or 3.1 μM, of glucose was oxidized to CO_2. Since 0.08 μM of glucose was oxidized by the citric acid cycle, the amount of carbon dioxide produced by direct oxidation appears to be 3.1-0.08, or 3.0, μM. This approximation leads one to conclude that in lens the direct oxidative pathway is 3.0/0.48, or about six times, more active than the citric acid cycle in the production of carbon dioxide. Similar conclusions can be drawn using the results obtained from cat and rabbit lenses.

To determine whether the artificial medium favors the oxidation of glucose by the alternate route, a comparison was made on the oxidation of 1-C^{14} and 6-C^{14} glucose in Krebs-Ringer buffer, phosphate buffer, and bovine aqueous humor. As recorded in Table 3, it appears significant that the carbon-1 oxidation is increased by 20% when lens is incubated in aqueous humor, as compared with the Krebs-Ringer buffer. The possible reasons for this stimulation of the oxidation of C-1 of glucose observed in aqueous humor will be discussed in the section on the "Reoxidation of Reduced TPN." In phosphate buffer the oxidation of both C-1 and C-6 is lower than in Krebs-Ringer buffer.

On the basis of these data, it would appear that the pattern of the aerobic phase of glucose metabolism is different in lens than in other tissues. The results seem to indicate

that in lens the direct oxidative pathway accounts for most of the carbon dioxide produced from glucose.

Comparison of the Activities of the Glycolytic and Direct Oxidative Pathways.—In the interpretation of the results in Table 3, it was assumed that most of the glucose was metabolized by the glycolytic pathway, so that lens provided sufficient amounts of pyruvate for the citric acid mechanism. It was important to demonstrate this fact and to contrast the relative extent of the glycolytic and direct oxidative pathways in lens. For this purpose, the radioactivity incorporated in lactic acid was determined when labeled C-1 or C-6 glucose was used as the substrate. The results are shown in Table 4.

TABLE 4.—*Incorporation of Glucose-C^{14} into $C^{14}O_2$ and C^{14} Lactate by Bovine Lens*

Total cpm Recovered in:	From 1-C^{14} Glucose	From 6-C^{14} Glucose	Ratio C-1/C-6
(1) CO_2	1,320 ± 150	31 ± 7	43
(2) Lactate	4,570 ± 240	5,810 ± 284	0.79
Sum of (1) + (2)	5,920	5,841	

Incubation medium contained 20 μM/ml. of glucose in 8.0 ml. of Krebs-Ringer buffer with the specific activity of either form of glucose at 402 cpm/μM. The values given are the mean plus or minus the standard error in cpm/4 gm. of wet weight/4 hr.

By the direct oxidative route, as shown in Figure 3, the carbon-1 atom of glucose is directly converted to CO_2. It therefore seems reasonable to assume that the 4570 counts recovered in the lactate from 1-C^{14} glucose is derived solely from glycolysis. On the other hand, the radioactivity recovered in lactate from 6-C^{14} glucose is that contributed from both the direct oxidative and the glycolytic pathway. The ratio of C^{14} lactate from $\frac{\text{1-}C^{14}\text{ glucose}}{\text{6-}C^{14}\text{ glucose}}$ of 0.79 is taken as the approximate fraction of glucose metabolized via glycolysis. It appears, therefore, that for every four molecules of glucose utilized by glycolysis, one molecule of glucose is shunted through the direct oxidative route. It is interesting that the sum of the counts recovered in the lactate and CO_2 is approximately the same from the two forms of labeled glucose. It appears that the triose phosphates formed by the direct oxidative pathway are eventually converted to lactate. As shown in Figure 3, this might occur either directly or after resynthesis to hexose phosphate.

In the experiment shown in Table 4 the average of 12 experiments indicated that the amount of glucose utilized was 19.8 μM. From the total counts recovered in lactate and CO_2, 5880 cpm, it appears that 5880/402, or 14.7 μM of glucose, was converted to these products. This value represents 75% of the glucose utilized and leaves 25% unaccounted for.

Mechanism of Reoxidation of Reduced TPN.—From the previous experiments it appears that the citric acid cycle plays a minor role in the carbohydrate metabolism of lens, and the aerobic pathway of any significance is the direct oxidative cycle. In the shunt mechanism TPN is the coenzyme reduced, and the possible mechanisms which reoxidize this coenzyme was next investigated. It seemed important to establish this fact, since all the biological energy derived by this pathway is most likely involved in the reoxidation of reduced TPN. In other mammalian tissues it is believed that the reduced TPN is oxidized by the chain of respiratory enzymes involving the flavoproteins and the cytochromes. However, in the corneal epithelium, the reduced TPN formed in the oxidation of glucose-6-phosphate is capable of being oxidized by another enzyme, glutathione reductase.[2] This enzyme has previously been demonstrated to occur in lens by Van Heyningen and Pirie.[18] In presence of this enzyme oxidized glutathione (GSSG) is reduced to glutathione (GSH), and the TPNH, in turn, is oxidized to TPN. In lens homogenate, using a catalytic amount of TPN, a coupled oxidation-reduction reaction can occur when oxidized glutathione is incubated with either G-6-P or 6-PG. An example of this type of oxidation-reduction reaction when 6-PG is used as a substrate is given in Figure 4.

The dehydrogenase catalyzes the reaction between 6-PG and TPN. The TPN becomes reduced, and 6-PG is converted to P-5-P and CO_2. The glutathione reductase then

transfers the hydrogen and electrons from TPNH to GSSG, resulting in the conversion to GSH and TPN. The reoxidized TPN can again react with another molecule of 6-PG, and the same sequence of reactions is continued until the substrates are utilized. In lens homogenate such an experiment was carried out, and the reaction was followed by measuring the formation of CO_2, P-5-P, and GSH. The results, recorded in Table 5, show that 6.9 μM of GSSG was reduced and 7.2 μM of CO_2 released.

A similar amount of R-5-P was anticipated, but only 5.3 μM was recovered. Apparently the pentose phosphate was further metabolized, as evidenced by the 0.5 μM of heptulose detected. The presence of GSH-reductase can also be demonstrated by following the disappearance of reduced TPN spectrophotometrically when lens homogenate is incubated with GSSG and TPNH. These results indicate that the GSH-reductase is present in lens and can function to reoxidize TPNH formed in the direct oxidative pathway. However, for this system to function in lens, in place of the flavoproteins and cytochromes, some means must exist by which GSH is oxidized. Two possible mechanisms by which this can be accomplished have been reported. Dische and associates [16] have reported that the lens capsule is capable of oxidizing glutathione. Pirie and Van Heyningen [17] have recently shown that under certain conditions lens extract is able to effect the oxidation of GSH by dehydroascorbic acid.

TABLE 5.—*An Interaction of GSH-Reductase and PG-Dehydrogenase in Bovine Lens Homogenate*

	Micromoles
Oxidized glutathione reduced	6.9
Carbon dioxide released	7.2
Pentose phosphate formed	5.3
Sedoheptulose phosphate formed	0.5

The reaction mixture contained 15 μM of GSSG, 15 μM of 6-PG, 0.1 μM of TPN, dialyzed bovine lens homogenate (1.2 gm. wet weight) and 0.05 M tris-(hydroxylmethyl)-amino methane buffer, pH 7.5, to make the total volume 6 ml. After two hours of incubation at 37.5 C in N_2, the reaction mixture was terminated with 2.0 ml. of 40% trichloroacetic acid.

TABLE 6.—*Effect of Various Agents on the Oxidation of 1-C¹⁴ Glucose by Lens*

Compound Added	cpm Recovered in $C^{14}O_2$	% of Control
0	367 ± 14	...
0.01 M NaCN	240 ± 22	65
0.01 M Na azide	300 ± 12	82
0.01 M Oxidized glutathione	689 ± 95	188
0.01 M Dehydroascorbic acid	419 ± 18	114

Bovine lenses (two) were incubated in 8.0 ml. of phosphate buffer containing 20 μM/ml. of 1-C^{14} glucose, with a specific activity of 180 cpm/μM. The results are expressed as the mean plus or minus the standard error in cpm/4 gm. wet weight/4 hr.

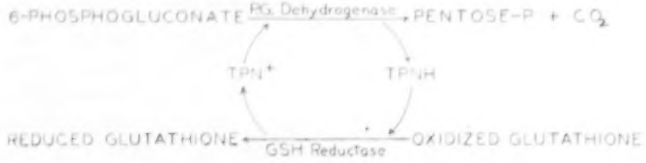

Fig. 4.—Coupled oxidation-reduction reaction.

To shed more light on the possibility that enzymes other than the flavoproteins and cytochromes are involved, it seemed worth while to determine what effect the addition of GSSG, dehydroascorbic acid, cyanide, and azide would have on the oxidation of 1-C^{14} glucose to CO_2. The results, as shown in Table 6, seem to indicate that, although inhibition is observed when either cyanide or azide is present in the reaction mixture, at the concentration used, almost complete inhibition would have been anticipated if the cytochromes were involved.

The GSSG stimulates the oxidation by 88%, presumably by increasing the rate of oxidation of TPNH. The presence of dehydroascorbic acid stimulates the oxidation by 14%. It is somewhat surprising to observe this stimulation in view of the lability of this compound under the conditions employed.[18] It should be recalled that, as shown in Table 3, the oxidation of C-1 of glucose in aqueous

humor was greater than that observed in other buffers. It is possible that the dehydroascorbic acid,[19] present in a poised system, makes this medium more favorable for increasing the availability of TPN, and thereby enhancing the oxidation.

The investigations of Pirie and Van Heyningen # and the evidence presented here lead one to speculate on the possibility that in lens, in place of the cytochrome system, the transfer of electrons from TPNH to O_2 may be accomplished by the sequence of events indicated in Figure 5. Slater [20] has proposed the possibility of these enzymes functioning in plant tissues. Of this scheme, the oxidation of TPNH by GSSG, catalyzed by GHS-reductase, definitely occurs in lens. There is suggestive evidence that dehydroascorbic acid oxidizes glutathione, although it is not known whether the reaction is mediated by an enzyme. The conversion of ascorbic acid to dehydroascorbic acid has not been demonstrated. Perhaps in situ the lens utilizes the dehydroascorbate furnished by the aqueous humor.

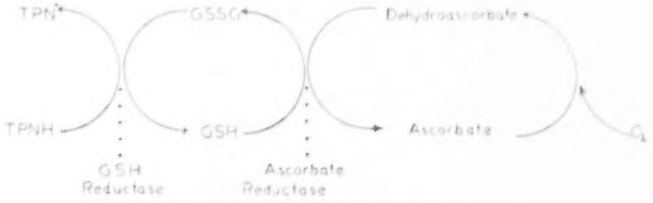

Fig. 5.—GSH-ascorbic acid oxidation mechanism.

There are reasons which favor the participation of the GSH-ascorbic acid oxidative mechanism in lens, rather than the cytochrome system. The high concentrations of glutathione and ascorbic acid in this tissue lend support to the possibility that such a mechanism exists. Moreover, since the direct oxidative pathway is the principal aerobic mechanism, only the reoxidation of TPNH need be considered. It seems more advantageous for the oxidation of the TPNH to take place in the soluble fraction of the cell, where the enzymes of the shunt mechanism are found. It has been shown that the glutathione reductase is found in the soluble fraction,[21] whereas the cytochrome system is known to be confined to the mitochondria. Since the lens is essentially acellular and mitochondria are most likely present in only small quantities, the reoxidation of TPNH by the cytochrome system would be extremely sluggish. It appears that a soluble and diffusible enzyme system would be more suitable for this purpose.

It is obvious that before the GSH-ascorbic acid oxidative mechanism can be established as playing a role in lens metabolism, further experimentation is necessary. Moreover, it is important to determine how much, and in what steps, biological energy, in terms of high-energy phosphate bonds, can be derived by such a mechanism.

References 15 and 17.

SUMMARY AND CONCLUSIONS

The metabolism of glucose in lens proceeds mainly by the glycolytic mechanism. However, the aerobic phase of glucose metabolism in lens is different from that of other tissues. The production of carbon dioxide from glucose is largely effected through the direct oxidative pathway, with little participation by the citric acid cycle. The possibility of an alternate mechanism for the reoxidation of reduced TPN is presented.

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The Optic Nerve Sheath Pathway

Its Role in Spread of Foreign Bodies and Tumor Cells from Cranial Cavity to Orbit

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Anatomical and injection studies upon cadavers have demonstrated the continuity of the cranial subdural and subarachnoid spaces with the corresponding spaces around the optic nerve.* Experiments with living animals have shown that colloidal material and nondiffusible dyes injected in the cranial subarachnoid space reach the optic nerve sheath.† It is generally accepted that intracranial cerebrospinal fluid pressure is transmitted to the eye through the subarachnoid space around the optic nerve.[7] Transmission of particulate matter through the optic nerve sheath in vivo is suggested by filling of the sheath with inflammatory cells in cases of meningitis.[7] However, there is controversy as to whether blood from an intracranial subarachnoid hemorrhage fills the optic nerve sheath by direct extension[3] or whether the optic nerve sheath hemorrhages in this condition are a secondary phenomenon due to increased venous pressure.‡

The following three cases are presented because they provide some additional evidence for the transmission of particulate matter through the optic nerve sheath in vivo.

REPORT OF CASES

CASE 1.—A. A., a 53-year-old white man, had headache and disturbance of speech, mentation, and gait for six months. Craniotomy, in June, 1954, revealed a left temporal lobe tumor. He died three months later.

Autopsy revealed a malignant glioma involving the entire left temporal lobe. The dura at the craniotomy site was indurated and contained suture material. Microscopically the dura contained many foreign body granulomas, with clusters of macrophages and multinucleated giant cells engulfing frag-

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* References 1 to 3.

† References 4 to 6.

‡ References 2 and 8.

Fig. 1.—Foreign body granuloma in dura. Under polarized light the fragments of suture material are bright, whereas the giant cells are dark. Reduced to 60% of mag. × 350.

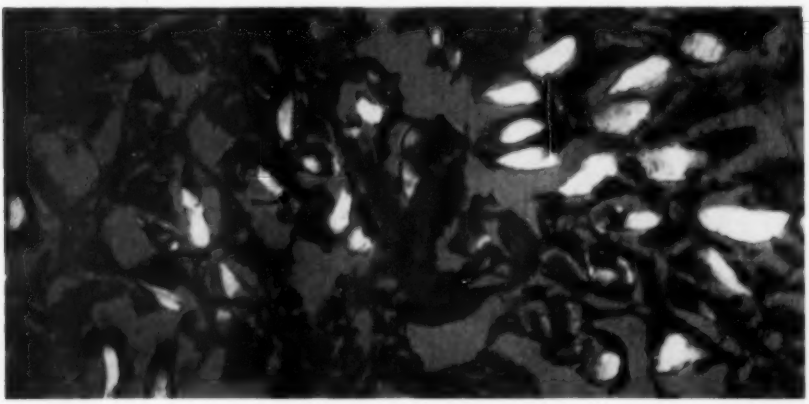
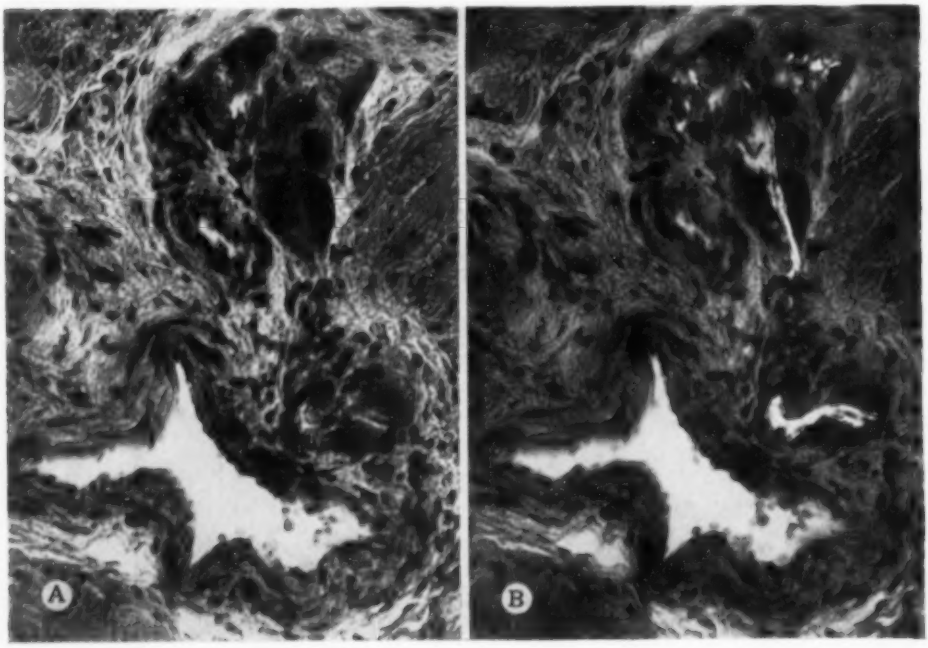


Fig. 2.—Optic nerve head, showing papilledema. The foreign body granuloma is in the sclera in relation to a group of vessels (arrow). Reduced to 67.5% of mag. × 55.

Fig. 3.—High-power view of foreign body granuloma in sclera under ordinary light (*A*) and under polarized light (*B*). The empty lumens of the artery in the lower part of the photograph and the arteriole just above center transmit light in both photographs, whereas the optically active foreign fibers in giant cells appear bright only under polarized light. Reduced to 72% of mag. × 350.



ments and strands of suture material. The suture fragments were grayish-pink in hematoxylin-eosin preparations and appeared bright against a dark background with polarized light (Fig. 1). A single fragment of similar birefringent material in a giant cell was found in a section of cerebral arachnoid near the tumor. None was noted in sections of the tumor, the optic chiasm, or the other organs except the eye.

Eye Findings.—Both eyes showed papilledema. A foreign body granuloma was found in the sclera of the left eye, 0.5 mm. from the end of the optic nerve sheath (Fig. 2). In 5 out of 13 sections of this eye there were multinucleated giant cells in a cluster near a group of small vessels which constituted part of the arterial circle of Zinn-Haller. The giant cells contained irregular fragments and strands of foreign material, which appeared bright when viewed under polarized light (Fig. 3).

Comment.—We can find no explanation for the optically active material in the scleral granuloma other than its representing fragments of suture material or some other foreign fiber introduced into the cranial cavity during the craniotomy. No other source of foreign material was present. The only likely pathway from cranial cavity to eye was the optic nerve sheath. Both subdural and subarachnoid spaces were possible avenues, since the arachnoid was left open after surgery and the two spaces were in communication. It seems doubtful, in a supine patient, that the force of gravity would direct particles to the end of the optic nerve sheath. In experimental animals a flow of cerebrospinal fluid toward the eye has been demonstrated, and the passage of Thorotrast and India ink particles through the dura-arachnoid sheath of the optic nerve has been shown.§ If such a mechanism exists in man, or if it occurs with increased intracranial pressure, it would help to account for the findings in this case.

Case 2.—S. L., a 65-year-old white woman, had a left radical mastectomy for carcinoma of the breast in 1953. One and one-half years later she developed headache, ataxia, and papilledema, and she was given radiation to the occipital area. A craniotomy revealed metastatic tumor. The patient died two months later.

Autopsy revealed metastases restricted to the central nervous system. There were metastatic nodules in the left parietal lobe and cerebellum, both involving overlying leptomeninges. The cerebral and spinal leptomeninges (including the areas around the optic chiasm) were diffusely infiltrated by metastatic tumor.

Fig. 4.—Carcinomatous infiltration of arachnoid, pia, and dura of optic nerve sheath. Reduced to 57% of mag. × 30.

Eye Findings.—Both eyes showed minimal papilledema. All sections showed diffuse carcinomatous infiltration of pia and arachnoid of the optic nerve sheaths without invasion of the optic nerves and with only superficial involvement of the dura (Fig. 4). The tumor cells were polygonal, columnar, or irregular in shape, and closely packed in cords and groups. The cytoplasm was scanty, while the nuclei were large, pleomorphic, and hyperchromatic. Bizarre giant forms and mitotic figures were frequent. The tumor infiltration reached the end of the optic nerve sheaths, and tumor cells were seen extending into the sclera for a short distance, to reach the adventitia of some of the small vessels seen in this location. The right eye showed tumor cells in the retro-orbital connective tissue and cytoid bodies in the nerve fiber layer of the retina near the papilla.

Comment.—The neoplastic infiltration was part of a generalized leptomeningeal carcinomatosis which probably spread from the brain down the optic nerve sheath. The possibility that the bilateral optic nerve sheath involvement resulted from independent blood-borne metastases cannot be excluded, although it seems much less likely. It is of particular interest that the invasion of sclera is in the same area in which, according to our hypothesis, the foreign material in Case 1 may have traversed the

§ References 5 and 6.

Fig. 5.—Clump of dark-staining tumor cells lying among the arachnoidal trabeculae at the end of the optic nerve sheath. Reduced to 44% of mag. × 100.

dural sheath. Only a few cases of cerebrospinal leptomeningeal carcinomatosis with involvement of optic nerve sheath have been reported previously.[9]

Case 3.—S. L., a 53-year-old white woman, had a right radical mastectomy (1936) and a left radical mastectomy (1946) for carcinoma. Metastases were discovered in the lungs by x-ray and in lymph nodes by biopsy in 1948. Radiation therapy was given. The patient died four months later.

Autopsy revealed widespread metastases in lymph nodes and abdominal and thoracic viscera. There were many metastatic nodules in the cerebrum and cerebellum, with extension into the leptomeninges.

Eye Findings.—Scattered in the interstices of the arachnoidal trabeculae of the optic nerve sheath there were a number of small clumps of tumor cells. The cells were large and irregular with dark pleomorphic nuclei, prominent nucleoli, and mitotic figures, similar to the tumor seen elsewhere. The clumps were found adjacent to dura, adjacent to optic nerve pia, or among the arachnoidal trabeculae; but all seemed to be lying free, without invading the tissues. The largest clump was found abutting on the sclera at the end of the optic nerve sheath (Fig. 5). There was a small metastatic nodule in the choroid. There was no evidence of papilledema.

Comment.—As in Case 2, the tumor cells in the optic nerve sheath probably originated in cerebral leptomeninges and traversed either subarachnoid or subdural spaces in the optic canal. In Case 2 the tumor may have infiltrated the meninges progressively to reach the eye. In this case the tumor cells lie free and probably reached the eye by floating in cerebrospinal fluid. A flow of fluid toward the eye, if such exists, would have facilitated the passage.

SUMMARY

A case of foreign body granuloma of the sclera near the optic nerve sheath and two cases of metastatic carcinoma of the optic nerve sheath are presented. The histologic findings are interpreted as indicating a transmission of particulate matter from cranial cavity to orbit via the optic nerve sheath.

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Evisceration of the Eye with Implantation of Polyvinyl Sponge

An Experimental Study

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In recent years ophthalmologists have been increasingly interested in surgical procedures designed to improve the cosmetic appearance of the face and orbit among patients who have undergone enucleation of an eye. These surgical procedures have been concerned either with the implantation of some material into the orbit as a substitute for the eye that was enucleated or with the insertion of some substance into the scleral envelope following the evisceration of the contents of the eye. In either case the implant served as a base over which a prosthesis could be fitted, the prosthesis having more motion on ocular rotation than was possible without such an implant.

Since the publication of Mules' original report,[1] in 1885, many modifications of the evisceration procedure have been described.*

The list of implant materials used in conjunction with evisceration has included such diverse substances as silver, gold, lead, aluminum, paraffin, cartilage, preserved tendon, Vitallium, tantalum, and acrylic. Guyton,[9] in a comprehensive review of this subject, has outlined the advantages and disadvantages of this operation, as well as its indications and contraindications.

One of the major problems encountered with the use of either intrascleral or intraorbital implants is their extrusion, either early or late in the postoperative period. These extrusions seem to be due to the tendency of the orbital and ocular tissues to react to an implant as to any foreign body. This occurs in spite of the so-called "inertness" of the implant material. There is very little, if any, continuity between such an implant and the surrounding tissues.

The solution to the problem of extrusion of implants would seem to lie in finding a substance which would become totally united with and incorporated into adjacent living tissue, thus militating against any possibility of extrusion in the future. At the same time, to be entirely suitable, such an implant material would have to satisfy criteria of nonabsorbability, stability, and biologic inertness. That such a substance fulfilling all the stated criteria might exist was first suggested by the work of Grindlay and Waugh.[10] They reported on a substance, polyvinyl-formal sponge (surgical Ivalon sponge),† which they used to repair tissue defects experimentally created in dogs at various anatomic sites. During the past several years polyvinyl sponge has been extensively used

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Fellow in Ophthalmology, Mayo Foundation (Dr. Donin). From the Section of Ophthalmology (Dr. Henderson) and the Section of Surgical Research (Dr. Grindlay), Mayo Clinic and Mayo Foundation. The Mayo Foundation, Rochester, Minn., is a part of the Graduate School of the University of Minnesota.

* References 2 to 8. Hall, E., quoted by Wood,[2] pp. 4464-4465. Huizinga, J. G., quoted by Wood,[2] pp. 4465-4468.

† The polyvinyl-formal sponge (Surgical Ivalon Sponge) used in this study was furnished by the manufacturer, Ivano Inc., Chicago.

Data on Implantation of Polyvinyl Sponge in Eye

Animal	Type of Incision	Ocular Tissues Removed	Polyvinyl Sponge: No. Pieces	Polyvinyl Sponge: Total Diam., Mm.	Penicillin (100,000 Units) in Sponge	Observation Period After Evisceration	Behavior of Eye
1	Circumlimbal	All except sclera	1	12	Yes	12 mo.	Sponge retained
2	Semicircular corneo-scleral	All except cornea and sclera	2	20	No	5 wk.	Animal died; eye became necrotic
3	Radial incision 5 mm. in length in sclera just behind limbus	Some vitreous	2	20	No	4½ mo.	Slight irregular haze present in cornea; sponge retained
4	Meridional incision in sclera 5 mm. in length over pars plana	Some vitreous	1	16	No	12 mo.	Cornea completely transparent; sponge retained
5	Semicircular corneo-scleral	Lens and most of vitreous	1	16	Yes	8 wk.	Sponge extruded
6	Semicircular corneo-scleral	All except cornea and sclera	2	27	No	12 mo.	Cornea completely transparent; sponge retained
7	Circumlimbal	All except sclera	1	18	Yes	12 mo.	Sponge retained
8	Semicircular corneo-scleral	All except cornea and sclera	2	28	Yes	3 wk.	Sponge extruded
9	Semicircular corneo-scleral	Lens and some vitreous	3	23	Yes	12 mo.	Cornea opaque on nasal side but transparent on temporal side; sponge retained
10	Radial incision in sclera 3 mm. in length over pars plana	Some vitreous	1	10	No	12 mo.	Cornea completely transparent; sponge retained
11	Semicircular corneo-scleral	All except cornea and sclera	3	45	Yes	12 mo.	Minimal over-all haze of cornea with minimal vascularization; sponge retained
12	Circumlimbal	All except sclera	2	30	No	30 wk.	Sponge extruded
13	Vertical corneal	All except cornea and sclera	3	30	No	12 mo.	Diffuse dull-gray haze to cornea with diffuse vascularization; sponge retained
14	Horizontal corneal	Lens and vitreous	3	27	Yes	12 mo.	Half of cornea showed faint haze and minimal vascularity; other half of cornea transparent; sponge retained
15	Semicircular corneo-scleral	All except cornea and sclera	2	33	Yes	3 wk.	Sponge extruded
16	Radial incision over pars plana	All except cornea and sclera	3	41	No	4 wk.	Sponge extruded
17	Radial incision over pars plana	Some vitreous	3	17	Yes	7 mo.	A few scattered opacities in cornea; sponge retained
18	Vertical corneal	All except cornea and sclera	3	42	Yes	12 mo.	Cornea transparent centrally but some haziness and vascularization in periphery; sponge retained
19	Semicircular corneo-scleral with conjunctival flap	All except cornea and sclera	2	20	Yes	12 mo.	Cornea completely transparent; sponge retained
20	Radial scleral 4 mm. in length just posterior to limbus	All except cornea and sclera	2	20	Yes	12 mo.	Some vascularization in center of cornea, otherwise transparent; sponge retained

to replace and reinforce tissue defects in humans under a variety of circumstances.‡ The present study was undertaken to determine the reaction of ocular tissues of the dog to the presence of this plastic sponge material.

THE STUDY

Evisceration of the globe (with various modifications) was carried out on the left eye of 20 dogs, followed by the implantation within the eyeball envelope of pieces of polyvinyl sponge. All the operations were performed with the animals under general anesthesia, and sterile technique was maintained during the performance of the operative procedures. The salient features of the operations that were performed are outlined in the Table.

Disregarding the incisions used, the 20 operations could be subdivided into four groups, as follows:

1. Evisceration with amputation of cornea and implantation of sponge into sclera, 3 cases.
2. Evisceration with cornea left intact, 10 cases.
3. Partial evisceration (lens and vitreous only removed), 3 cases.
4. Sponge implanted directly into the vitreous cavity without removal of any tissue except vitreous, 4 cases.

Four and a half months after operation, the eye of Animal 3, in which the sponge had simply been introduced into the vitreous cavity and successfully retained, was enucleated. This was done to determine the reaction of the ocular tissues to the presence of the sponge after such a period of time. Similarly, the eye of Animal 17, in which an identical procedure had been performed, was removed after seven months. Twelve additional animals in which the intrascleral implants were successfully retained were kept under observation for an average period of one year, after which the left eyes were enucleated and examined histologically. One animal that had been in poor general health prior to surgery on the eye died five weeks postoperatively. Extrusion of the implant occurred in the remaining five animals.

Observations.—Before enucleation of the left eye of the 14 animals in which the polyvinyl sponge was successfully retained, an examination was made with special reference to the over-all size and condition of the eye as compared with the right eye, which was used for control. Particular attention was given to the status of the cornea of those eyes in which a corneal amputation had not been a part of the evisceration procedure (12 eyes). It was found that in practically all of these eyes, except those completely eviscerated, the eye retained its normal shape and size (Fig. 1). In nearly half (five eyes) the cornea was entirely transparent, so that the polyvinyl sponge was visible in the interior of the eye. Several of these eyes with transparent corneas at the time of enucleation had had vascularization and clouding of the corneal stroma in the first several months after evisceration. None of the corneas in the entire group of 12 eyes was entirely opaque.

Fig. 1.—(*a*) Sponge implant visible through transparent cornea; (*b*) control eye. Note that the eyes are equal in size.

‡References 11 to 14.

The two eyes that had been enucleated at four and a half and seven months respectively showed minimal haze of the cornea, and it was possible that the percentage of transparent corneas would have been greater had these eyes been kept under observation for a year. Neither the type of surgical incision nor the status of the eye relative to the amount of tissue that was eviscerated seemed to have any influence on the degree of corneal transparency.

On enucleation, the 14 eyes were subjected to a closer scrutiny. In the majority of them (10 eyes) the color of the polyvinyl sponge had changed from white to light brown. In the remaining eyes the sponge varied from shades of gray to black. In all eyes but two the consistency of the sponge was slightly firmer than at the time of insertion, but there was no loss of resiliency. In the two eyes excepted, the sponge seemed to be undergoing a softening process, or necrosis, in the center. When stained with hematoxylin and eosin and examined under the microscope, the polyvinyl sponge (except in the two eyes) was uniformly stained a light blue and had a foamy appearance. A sprinkling of calcium deposition was present within the sponge in all specimens. The spaces demarcated by the sponge trabeculae were filled with cellular tissue, which exhibited a syncytium-like arrangement. Continuity between adjacent spaces of the sponge was established by passage of this cellular tissue through tiny breaks in the framework of the sponge. In all specimens the endothelium of the cornea was absent. This was surprising in view of the high degree of transparency noted on gross examination. In some specimens with Descemet's membrane intact the endothelium was replaced by fibrous connective tissue, and in other specimens this connective tissue was slightly vascularized. In those eyes in which Descemet's membrane had been disrupted by reason of the incision through the cornea, the stroma of the cornea had become continuous with the connective tissue which lined the interspaces of the polyvinyl sponge. With these observations most of the similarities in the behavior of the sponge within the eye cavities of all specimens were covered. Certain dissimilarities then became evident between the eight eyes in which a total evisceration with or without preservation of the cornea had been performed and the six eyes in which only a partial evisceration (removal of lens and iris, or vitreous) was done.

In the former group, of eight eyes, the polyvinyl sponge filled the cavity of the eye completely and compactly (Fig. 2) and was firmly adherent to the wall of the sclera (Fig. 3). The spaces of the sponge framework were filled with connective tissue consisting of collagen fibers and flattened fibroblasts. Neither inflammatory cells nor giant cells could be seen in the sclera or the tissues within the framework of the sponge. In one eye of this group (Animal 13) the sponge framework was somewhat moth-eaten in appearance, and deposition of calcium was unusually heavy. Hemorrhage was a prominent feature throughout the specimen, with masses of red blood cells in all phases of absorption and organization. An increase in the number of polymorphonuclear leucocytes, lymphocytes, and macrophages was evident, as compared with the other eyes of this group.

Fig. 2.—Sagittal section of eye with sponge implant.

In the latter group, of six eyes, on the other hand, the spaces in the sponge were filled with a connective tissue containing in-

flammatory cells, pigment granules, giant cells, and fibroblasts possessing plump nuclei. In one specimen a localized area of osteoid tissue with minimal formation of bone was present. Furthermore, except for one specimen (Animal 14), the sponge in this group did not completely and compactly fill the cavity of the eye, as in the group which had undergone more complete evisceration. The sponge filled only the anterior two-thirds of the vitreous cavity and was adherent to parts of the ciliary body and the anterior portion of the retina and choroid. More posteriorly the retina was detached and adherent to the posterior surfaces of the sponge. In these specimens the component layers of the retina were intact except for the layer of rods and cones, which had disappeared. In some areas the internal limiting membrane of the retina could be seen, but in other areas this membrane had disappeared, so that a fibrous connection was established between the nerve fiber layer of the retina and the connective tissue within the spaces of the sponge (Fig. 4). In the one exception (Animal 14) the sponge completely filled the vitreous cavity and the retina was not detached, but it was in this eye that the largest piece of sponge had been inserted. In general, in all specimens in which the lens had not been eviscerated, spontaneous absorption of the majority of the lens substance had occurred. In one specimen (Animal 17), in which the eye was removed at the end of a seven-month period, the signs of inflammatory reaction were more marked. This eye showed evidence of both recent and old hemorrhage, and the over-all microscopic appearance was very similar to that of the eye removed from Animal 13, which was described in the previous paragraph.

As mentioned previously, the polyvinyl sponge was extruded from the eyes of five animals (Animals 5, 8, 12, 15, and 16). The path of the extrusion was through the cornea, and extrusion occurred in from three to eight weeks following evisceration. We could not definitely determine whether the incision line in the globe served as the initial point for the extrusion of the sponge. The type of incision, the size of the sponge implanted into the eye, the presence or absence of penicillin in the interstices of the sponge, and the extent of the evisceration procedure did not seem to be factors that influenced the question of extrusion. The most striking feature of these eyes was the marked inflammatory reaction of the wall of the globe, as compared with the eyes in which extrusion of the sponge had not occurred. At the edges of the break in the cornea the tissues were nearly necrotic; the choroid showed a diffuse thickening due to infiltration with polymorphonuclear leucocytes, giant cells, and lymphocytes. In two specimens abscess formation was present on the surface of the sponge. The sponge itself did not appear deteriorated.

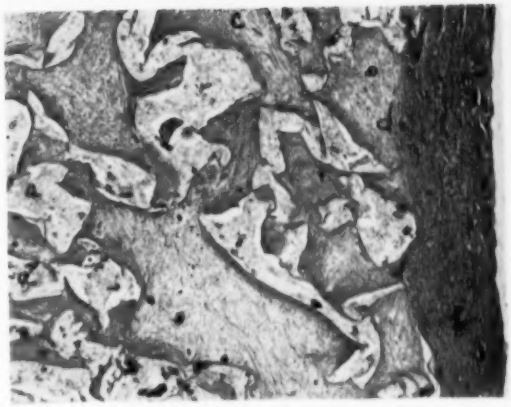

Fig. 3.—The connective tissue lining the interspaces of the sponge is continuous with the fibrous lamellae of the sclera. (*a*, *a'*) Sponge; (*b*) sclera; (*c*) connective tissue lining sponge; (*d*) connective tissue continuous with sclera. Reduced 15% from mag. ×40.

Fig. 4.—In areas where the internal limiting membrane is absent, the connective tissue within the interspaces of the sponge has become continuous with the tissues of the retina. (*a*) Sponge; (*b*) retina; (*c*, *c'*) connective tissue lining sponge and continuous with retina. Reduced 15% from mag. ×40.

COMMENT

In an over-all evaluation of results, it seems reasonable to say that, of the 19 animals in which the study was of sufficient duration to warrant conclusions, the polyvinyl sponge was successfully retained in 12. Among the remaining seven animals, the sponge was extruded in five, and in two (Animals 13 and 17) the inflammatory reaction was so marked and the union of connective tissue with the sponge so incomplete as to lead us to consider the outcome unsatisfactory, even though the sponge was not extruded.

The striking feature of the eyes in which the sponge was successfully retained was the manner in which the interstices of the sponge became filled with connective tissue. This connective tissue, in turn, was continuous with the ocular tissues of the wall of the eye, suggesting that a permanent bond had been forged between the ocular tissue and the foreign substance. This tendency for polyvinyl sponge to become an integral part of the tissues into which it was placed was noted by one of us (J. H. G.) [10] in previous experimental work with tissues other than the eye. The tolerance of ocular tissues to this sponge material (particularly in the eyes in which only vitreous was replaced by sponge) is even more amazing when one considers how intolerant are the ocular tissues of humans to almost all types of intraocular foreign substances. Even foreign bodies, such as small pieces of glass, that are tolerated by ocular tissues never become an integral part of the eye but are, instead, walled off. So intolerant are ocular tissues, particularly the uveal tract, to trauma, as well as to foreign bodies, that in humans it is always recommended that the uveal tissues be carefully eviscerated before any type of implant is placed in the scleral envelope. In this experiment, we did not remove the uveal tissues of some of the dogs' eyes so as to determine whether a condition similar to sympathetic ophthalmia of humans might develop. At no time did we observe any difficulties with the control eyes of these dogs. However, as pointed out by Nicolas,[15] sympathetic ophthalmia may not occur in dogs or other domesticated animals. As a further comment on the behavior of this sponge, it is to be remembered that among the dogs in which the uveal tissue was removed prior to insertion of the sponge there was even less reaction to the presence of the foreign substance.

Another noteworthy feature of these eyes in which the polyvinyl sponge was retained was the tendency of the corneas to regain their transparency with the passage of time, even though the endothelium was consistently absent and the corneal stroma in many instances was continuous with the connective tissue that filled the interspaces of the sponge. This was a surprising finding, and a rather contradictory one, in view of the widely accepted hypothesis of Cogan and Kinsey [16] that the corneal stroma of the living eye is clear because it is in a state of deturgescence through osmosis, the epithelium and endothelium acting as semipermeable membranes. Bock and Maumenee,[17] however, found that a layer of corneal stroma in the eyes of rabbits would remain clear for at least 48 hours, even though the tissue was isolated from both endothelium and epithelium. They felt, on the basis of this work, that deturgescence was not entirely dependent on osmotic interchange through an intact epithelium and endothelium. In further observations over a longer period of time, these investigators then found that corneal stroma would eventually deteriorate if separated from endothelium and aqueous, even though a connection with the limbus remains. The clearing of the corneas of our dogs over a period of one year certainly would require some explanation other than the presence of an endothelium, and this entire problem could serve as an additional subject for research, using the polyvinyl sponge as a substitute for the endothelium.

On inspection of the polyvinyl sponge in these specimens in which it had been successfully retained, very little change was noted in the size and the resiliency of the material as compared with its character prior to implantation within the eye. The explanation

for the change in color from white to brown in most specimens was not found.

The presence of calcium throughout the sponge was not regarded as unusual, and the actual demonstration of bone formation in one specimen brings up the possibility that bone would have formed in other eyes had the observation period prior to enucleation been more prolonged.

What of the failures? In those instances in which the implant was extruded the failure seemed due to secondary infection. It was reasoned that the secondary infection produced a necrosis of some part of the wall of the globe and the sponge was extruded as the result of exteriorization. The sponge itself in these instances seemed unaltered by the marked inflammatory reaction surrounding it. It should also be pointed out that the postoperative care of all the dogs was not conducive to the maintenance of asepsis, such as is customary with intraocular operations among humans.

In the two eyes (Animals 13 and 17) in which the microscopic picture was considered unsatisfactory, even though the sponge was retained within the eye, hemorrhage was considered to be the complicating factor.

In all eyes, regardless of whether extrusion or retention of the polyvinyl sponge had occurred, an attempt was made to correlate the behavior of the eyes with the type of incision that was made in the wall of the globe and with the number and size of the pieces of sponge that were inserted. No relationship of these factors to the behavior of the eyes could be found.

On the basis of the present investigations, supplemented by the reports of others § who have used this sponge in orbital tissues, the possibility of implanting this substance into the eyes of humans arises. Such an occasion might arise in ophthalmic surgery wherein it seemed practical to eviscerate the contents of the eye, yet retain as much as possible of the contour and wall of the eye, with its muscles still attached to serve as a mobile stump to which a prosthesis could be fitted. If such a situation were to go beyond the stage of speculation, it is our feeling that the polyvinyl sponge would be well tolerated by such an eye providing hemorrhage could be well controlled and secondary infection avoided.

§ References 13 and 14.

SUMMARY

The left eyes of 20 dogs were either partially or completely eviscerated. Polyvinyl sponge was then inserted into these eyes, and their behavior was observed over variable periods of time up to one year. In the majority of eyes the sponge was successfully retained. In such specimens the interspaces of the sponge became filled with a connective tissue that was continuous with the tissues comprising the wall of the eye. These eyes showed a remarkable tolerance toward this sponge, and in several cases the corneas became transparent over an observation period of one year.

In those eyes in which either the sponge was extruded or the tissues exhibited an unsatisfactory reaction to the retained sponge, hemorrhage or secondary infection seemed to be the complicating factor.

The possible usefulness of polyvinyl sponge as an implant material among eyes requiring evisceration in humans is discussed.

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News and Comment

GENERAL NEWS

Course on Glaucoma.—A course on glaucoma, with particular emphasis on gonioscopy and the study of the anterior angle, will be given at the Brooklyn Eye and Ear Hospital on Nov. 14, 15, and 16, 1955. Ample opportunity for practical instruction in the use of the gonioprism will be given, and material from the glaucoma clinic will be utilized. The course will be given by Dr. Daniel Kravitz, assisted by Dr. Walter V. Moore, Dr. Mortimer A. Lasky, Dr. Harold Schilback, and Dr. Arthur Shainhouse.

Registration is limited to six ophthalmologists only. Application and the fee of $40 may be addressed to Dr. Daniel Kravitz, Brooklyn Eye and Ear Hospital, 29 Greene Ave., Brooklyn 38.

E. B. Dunphy Fellowship for Eye Research.—The Massachusetts Lions Eye Research Fund has created the E. B. Dunphy Fellowship for Eye Research. This Fellowship carries an annual stipend of $5000 and will be awarded on a yearly basis by a committee consisting of Dr. David Cogan, Dr. Charles Schepens, Dr. William Stone Jr., and Dr. Edwin B. Dunphy.

Anyone may apply, but the research must be conducted in Massachusetts. Applications for 1956 must be received by Nov. 1, 1955. Candidates should write to Dr. Edwin B. Dunphy, 243 Charles St., Boston, giving a short biography and two references. They should describe briefly the problem they are interested in and state whether or not they have adequate laboratory facilities for doing the work.

Memphis Eye, Ear, Nose and Throat Convention.—The annual Convention will be held Feb. 11, 12, and 13, 1956. Speakers will be Georgiana Theobald, M.D., Oak Park, Ill.; Alson E. Braley, M.D., Iowa City; Harvey E. Thorpe, M.D., Pittsburgh; Alden H. Miller, M.D., Los Angeles; David E. S. Wishart, M.D., Toronto, Canada, and Edmond Prince Fowler Jr., M.D., New York.

Lymphosarcoma of the Bulbar Conjunctiva

Report of a Case

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and
IRWIN GELERIS, M.D., New York

This report concerns itself with an instance of a very rapidly growing monofocal lymphosarcoma of the conjunctiva which was treated by means of a radioactive strontium (Sr^{90}) applicator. Biopsies of the affected conjunctiva were made before treatment was begun and after treatment was terminated, and it seems justifiable to consider the results as constituting a local clinical cure.

Submitted for publication June 14, 1955.

REPORT OF CASE

The patient is a 71-year-old Spanish woman who presented herself at regular intervals over a period of two years for visual difficulties due to incipient cataracts and for vague subjective complaints characterized chiefly by burning and irritation of the conjunctivae of both eyes. She was seen by several independent observers, who found nothing unusual other than the lens changes mentioned and a mild hyperemia of the conjunctival surfaces.

On Feb. 1, 1954, she returned, complaining of greater annoyance from the irritation of the lids, and at that time two separate thickenings of the lower bulbar conjunctiva of the left eye were noted. They were roughly about 10 mm. in diameter and

Fig. 1.—Lymphosarcoma of bulbar conjunctiva.

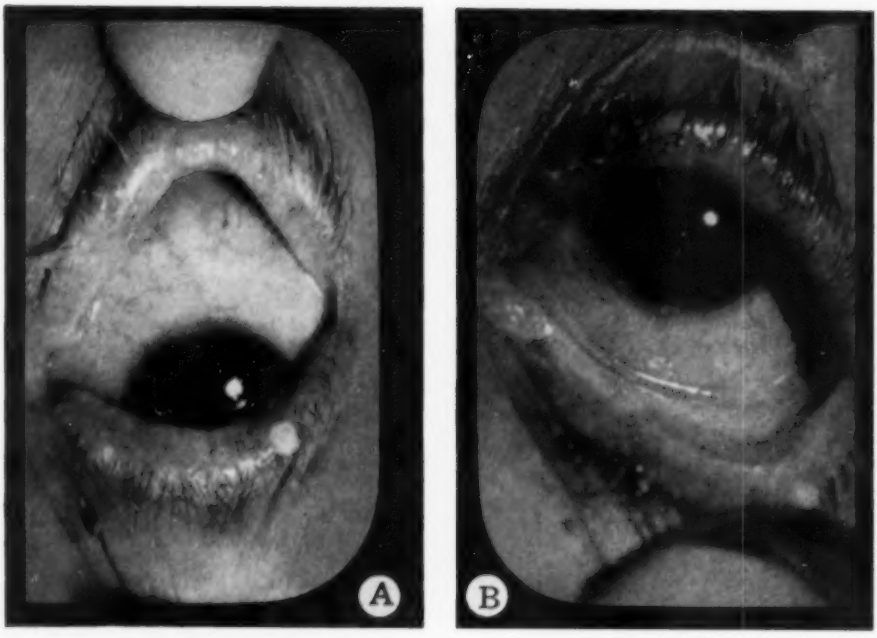


Fig. 2.—Lymphosarcoma of bulbar conjunctiva following treatment with Sr^{90} applicator. *A*, upper fornix; *B*, lower fornix.

occupied about half of the ocular conjunctiva below the horizontal level. They were separated by a narrow strip of normal conjunctiva. The tissue seemed suggestive of lymphoid structure, was pinkish in color, and was freely movable over the surface of the sclera. Growth was extremely rapid. Within four days the two islands of abnormal conjunctiva had coalesced and extended completely around the corneal circumference. The thickened tissue was still freely movable over the scleral surface. The margins of the cornea were overhung by the bulge of the infiltrated conjunctiva. The process covered the entire globe, but stopped at the upper fornix, while the lower fornix was invaded for a distance of some 3 mm. Specimens of the lower and upper conjunctivae were removed for biopsy.

No orbital masses were palpable; there was no limitation of ocular motility, and no glandular enlargements were noted in the region of the ear, neck, clavicle, or axilla. The right eye and adnexa were normal. General examination revealed no evidence of systemic lymphatic disease, and the blood picture and the cytologic study of the bone marrow also yielded no abnormal data.

The laboratory reports disclosed marked subepithelial lymphocytic proliferation with evidence of malignancy. The patient was referred to the department of radiology, where treatment with the Sr^{90} applicator was instituted. The following summary was prepared by the radiology department:

"The report from the pathology and laboratory departments of low-grade malignant lymphoma prompted us to consider the use of superficial radiation, best delivered in this case by the Sr^{90} beta applicator. Our particular applicator delivers, with recent calibration, 30 beta r per second. This applicator is produced by Tracer-Lab and contains the nuclear reactor fission product Sr^{90} with its radioactive daughter element yttrium (Y^{90}), having a half-life of 20 years and maximum beta energy of 218 mev.

"This method is especially indicated for superficial lesions of the anterior segment of the eye, since no gamma radiation is emitted. It has an advantage over radium D, where the dose at 1 mm. depth is 12%, whereas Sr^{90} at the same depth yields 50%. At a depth of 2 mm. or more, radium D would have little or no effect. Sr^{90} would probably be effective at 4 or 5 mm. This lesion is approximately 2 or 3 mm. thick in most areas.

"The patient was treated as follows:

3/5/54: In contact at the medial fourth at approximately 9 o'clock for 20 seconds, delivering 600 beta r.

3/23/54: 600 beta r was delivered at the right and left lateral aspects at 3 and 9 o'clock.

3/30/54: The above dose was repeated because of the minimal reaction.

4/9/54: Three separate areas were treated with some overlapping, but the strontium applicator was placed at approximately 10, 2, and 5 o'clock. Each area received 600 beta r. At this time the patient showed a definite lessening of the pain and a marked regression of the lesion.

4/23/54: It was decided again to treat three areas with 600 beta r each, in contact at approximately 3, 10, and 12 o'clock. Marked improvement was noted."

Treatment was begun 33 days after the disease was first noted and was continued at intervals over 18 days. A total of 6600 beta r was applied. To date, there have been no effects upon the lens which might be ascribed to stray radiation.

Microscopic Report.—Microscopic study of two biopsy specimens from the bulbar conjunctiva shows a marked proliferation of lymphoid cells in the subconjunctival stroma, extending into the overlying epithelium. The tumor consists of small and large round cells. The former have hyperchromatic nuclei and scanty cytoplasm, while the latter exhibit a pale cytoplasm and vesicular nuclei. The large cells also show irregularity of size and shape. Mitotic figures are evident, and cellular atypicality is noted. In areas cellular aggregates simulate germinal centers. The bulk of the tumor is made up of the small round cells. They have the characteristics of mature and immature lymphocytes. These cells are closely packed. There is no evidence of inflammatory residue. The tumor structure is dominantly that of a lymphocytic sarcoma.

Further Studies.—A critical clinical and laboratory study, including x-rays of the chest, abdomen, and bones; repeated hemograms, and bone marrow examinations, revealed no evidence of lymphocytic leukemia or lymphosarcoma in any other viscera. The tumor responded to radioactive strontium therapy, and subsequent biopsies of the conjunctiva showed a chronic inflammatory reaction, fibrosis, and no evidence of tumor.

Medical Summary.—The patient is an elderly, rather obese Spanish woman exhibiting the facies and early tremor of Parkinsonism. This is probably of arteriosclerotic origin, for evidence of generalized arteriosclerosis is readily observed. No abdominal masses are palpable. No lymphatic nodes are palpable. There is a diastasis of the abdominal recti. Blood pressure 110/84.

Representative Laboratory Findings.—Urine examination (June 15, 1954): Albumin negative; glucose negative; acetone negative; specific gravity 1.009; pH 6.0; red cells per HPF rare; white cells per HPF rare; casts—rare cylindroids and mucus threads; epithelium, a few squamous cells.

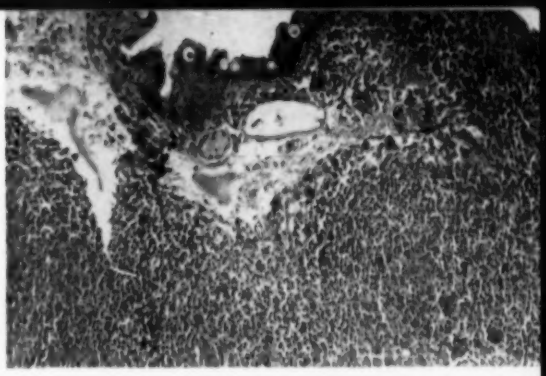


Fig. 3.—Photomicrograph of the conjunctiva and subconjunctival areolar tissues, showing extensive infiltration by neoplastic lymphomatous cells. Reduced to 60% of mag. × 100.

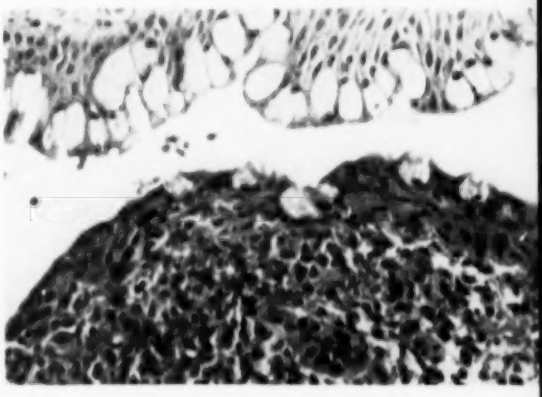


Fig. 4.—High magnification of Figure 3; reduced to 62% of mag. × 400.

Blood: Glucose, 91.3 mg. per 100 cc.; urea nitrogen, 14.3 mg. per 100 cc. (June 17, 1954).

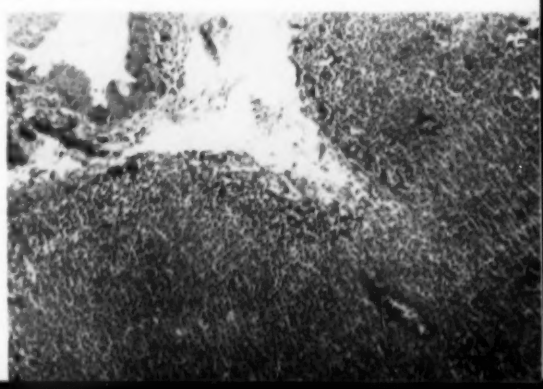
Sedimentation rate (June 18; Westergren scale)

	Mm.
15 min.	1
30 min.	4
45 min.	8
60 min.	14

Normal sedimentation rate, 5 mm. or less in 15 minutes; 15 mm. or less in 45 minutes.

Wassermann tests (June 15): Eagle-Wassermann negative; Eagle flocculation negative; Kahn negative.

Fig. 5.—Replacement of areolar connective tissue by neoplastic lymphocytic proliferation. Reduced to 62% of mag. × 100.



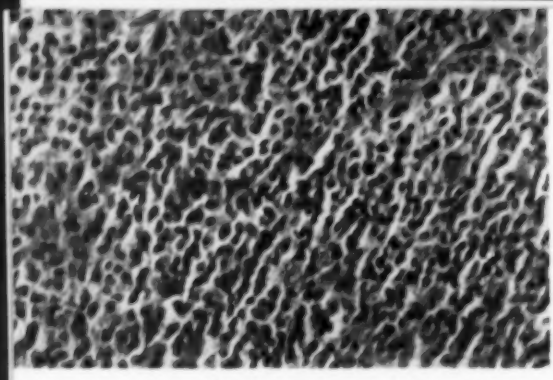


Fig. 6.—High magnification of Figure 5; reduced to 60% of mag. × 400.

Blood picture (June 21): Hemoglobin 15.3 gm. per 100 cc.; RBC 5,100,000; color index 0.9; WBC 7450.

Neutrophiles	62%
Immature	2%
Mature	60%
Eosinophiles	4%
Lymphocytes	29%
Monocytes	5%

Differential Bone Marrow Studies (June 28, 1954): Summary and diagnosis: The marrow is of normal cellular structure. The differential myelogram shows nothing significant. There is no evidence of leukemia, tumor, or lipoidosis. A few typical plasma cells are present, but only one of these is nucleolated.

Microscopic Study of Bone Marrow from Paraffin Section (June 29): Normal architecture.

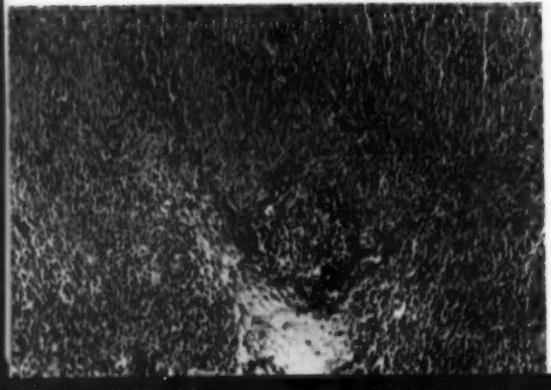
Electroencephalography (June 22): Normal.

X-Rays (June 17, 1954): Examination of the chest was made with the patient in the erect position. There is thickening of the cupola in both apices. Minimal fibrosis is seen extending into the right apex. The hilar shadows are somewhat thickened, with accentuation of the bronchovascular markings and peribronchial infiltration in both paracardiac regions. The right diaphragm shadow and costophrenic angle are clear. There is slight haziness of the left costophrenic angle, which may be the result of overlying soft tissue. The cardiothoracic ratio is just within the limits of normal. Slight elongation and tortuosity of the aorta are noted, with calcification of its transverse segment.

Examination of the abdomen was made. An anteroposterior view was taken with the patient in the supine position. The right kidney appears to be somewhat low in position. The left appears normal in size, shape, and position. The psoas muscle shadows are well delineated. There is no definite evidence of opacities in the region of the kidneys, ureters, or bladder.

Examination of the right leg, including the knee joint, was made. Anteroposterior and lateral views were taken. No osteal or periosteal process is noted.

Fig. 7.—Diffuse proliferation of neoplastic cells with loss of normal architecture at level just above sclera.



COMMENT

What is the present concept of lymphosarcoma?

Most workers in the problem feel that the disease is one of multiple origins. These may be extranodal or intranodal. A focus which is accessible to discovery may be considered primary and monocentric if no other foci are found, but actually this is a presumption, since it is never possible to exclude a lesion which might exist in a hidden locus. A so-called primary focus may be eradicated, but the disease almost invariably crops up 5, 10, or even 15 years later in another spot. When the sarcomatous involvement becomes sufficiently extensive, the tumor cells enter the blood stream in large numbers and the picture of leukemia supervenes.

Does the neoplasm metastasize?

Probably not. If cells do enter the blood stream or the lymphatic channels from the tumor, as they may during a biopsy, they are killed off by the phagocytes, which originate in the reticuloendothelial system. There is continuous vigilance on the part of the protective mechanisms of the body against invading tissue cells, and the maintenance of good health is possible when the virulence and the numbers of the invaders cannot tip the scales against the defensive capacities of the host. There is no definitive evidence that the tumor extends by way of the lymphatics or blood stream. Even locally, lymphosarcoma is not severely invasive but, rather, causes symptoms by pressure against neighboring structures through tumor enlargement. Only in the leukemias is the blood stream considered to have been invaded.

Should systemic therapy have been employed in this case to ward off systemic involvement?

No. The visible lesion was readily eradicated by simple and safe means. Nitrogen mustard, radioactive phosphorus, and x-rays applied systemically should not be used as prophylactic measures. In this particular case the life expectancy of the patient is shorter than the time of probable appearance of a systemic lesion.

Can a favorable prognosis as to future involvement be made because we have completely eradicated a primary focus?

No. Since the disease is one of multiple foci of origin, one must be reconciled to the expectation of future trouble in spite of having completely eradicated a primary focus. It may be that the primary involvement of some specific organs predisposes to a longer latent period before involvement elsewhere,* but actually we do not have enough cases on record to predict the outcome on the basis of organ origin. Some of the cases of innocent lymphomata which we occasionally see, usually in the lower conjunctival fornices, may years later prove to have been the unsuspected indicators of a sarcomatous disposition. Early, it is impossible to differentiate microscopically between the innocuous variety and the potentially malignant form. More complete and closer follow-up histories are essential. The meticulous reports of McGavic might well serve as models.

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Complete Removal of Gliomas Affecting the Optic Nerve

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and
HUGO L. BAIR, M.D., Rochester, Minn.

Gliomas, or so-called low-grade astrocytomas, affecting the optic nerves have for some years been of great interest to ophthalmologists and ophthalmic surgeons. Excellent contributions to the literature have been made by many authors concerning the pertinent pathologic aspects, classification, peculiarities of growth, and methods of treating these tumors.* Opinion has varied greatly as to the methods of treatment and the prognosis for life expectancy among patients harboring these tumors. The undeniable relationship of this tumorous growth with von Recklinghausen's disease in certain cases has tended to add confusion rather than to clarify the concepts of prognosis and necessary surgical approach and treatment.

Reflection on the subject, however, and a review of the writings of others make it evident that the prognosis in cases of glioma of the optic nerve depends on the extent and type of growth.† Obviously, a tumor involving the optic chiasm or the neighboring structures of the hypothalamus and third ventricle, or one which involves the optic chiasm and both nerves, is a lesion which offers an undeniably gloomy outlook both for the maintenance of useful vision and for the preservation of life over a long period. The rather discouraging reports in the literature concerning gliomas located in this portion of the optic pathways bear witness to this fact.* On the other hand, in those cases in which the tumors are located primarily within the orbital part of the optic nerve, or with some intracranial extension which is entirely prechiasmal, reports in the literature and our experience indicate a much more favorable prognosis.[11]

The large majority of these tumors encountered are of low-grade malignancy and therefore of a very slow-growing nature. They do not invade surrounding tissues and seem to extend centrally by propagation along the optic nerve. We are cognizant of the many reports concerning mere biopsy of these tumors in which long remission, as well as apparent cure, has occurred. However, because of the malignant nature of the tumor, often it has been deemed wise by many to sacrifice the ocular globe, and even to exenterate the orbit. In part this policy may have arisen, of course, from the ophthalmic expediency of obtaining necessary surgical room in approaching the optic nerve through the lateral or anterior approach, and in part from the desire to perform complete removal in the presence of a malignant lesion.

As neurosurgical transcranial approach to the orbit has become more practical, many neurosurgeons have become impressed with the necessity of approaching all these lesions for visual and definitive microscopic identi-

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* References 1 to 6.

† References 7 to 10.

fication, since, in certain cases, complete removal of the offending lesion may be accomplished with preservation of a normal-appearing eyeball—an eyeball, albeit, that is blind but that moves conjugately with its fellow of the opposite side.[12]

Although, as Byers has stated, somewhat less than half of the ocular globes, when severed from the optic nerve, may subsequently atrophy, still the approach to the orbit through the transcranial route often allows the surgeon to avoid trauma to the extraocular muscle cone, so that the blind eye may have satisfactory motion, and the over-all postoperative cosmetic effect will be pleasing to the patient himself.

Since, pathologically, it seems uncommon for the glioma of the optic nerve to invade the orbital tissue or to invade the optic disc, the problem arises concerning sacrifice of the globe and orbital exenteration. It has been our good fortune to see and treat four patients who have had glioma of an optic nerve and, by utilization of transcranial approach to the orbit and nerve, to resect completely the involved nerve distal to the optic chiasm on the same side and proximal to the ocular globe, thus removing the tumor in toto and sparing the ocular globe on the involved side.

REPORT OF CASES

Case 1.—This 3-year-old white boy was first seen at the Mayo Clinic in June, 1942. The parents had noticed that the patient's left eye had become more prominent during the two to three weeks prior to his admission to the clinic. The child had not experienced symptoms and had not complained of anything unusual. The parents said they had not noticed any evidence of visual disturbance. Because of the prominence of the eye, however, the child had been taken to the home physician, who had noticed that there was edema of the optic disc on the left side and early edema of the nerve on the right. The child's history was normal, and there was no evidence of familial disease.

General examination at the clinic showed the child to be well developed for his age. The blood pressure was 100 mm. of mercury systolic and 60 mm. diastolic; pulse and temperature were normal. The results of general examination were unremarkable except as they related to the eyes; definite proptosis was present on the left side. Neurologic examination revealed evidence of exophthalmos on the left side only. Detailed examination of the eyes showed the lids to be normal, but both eyeballs were rather prominent. The left ocular globe was 2 mm. more prominent than the right. The pupils were equal and reacted normally to light. The ocular rotations were normal, and examination of the optic fundi revealed a choking of the optic disc on the left of 5 D. and on the right of 1 to 2 D. The hemoglobin was normal, and the numbers of erythrocytes and leucocytes were within normal limits. Results of tests on blood serum were normal, as was the result of urinalysis. Nothing abnormal was noted on the roentgenograms of the skull and of the thorax.

The diagnosis of intraorbital tumor was made, and left transfrontal craniotomy was carried out. At operation an intracranial and intraorbital astrocytoma of the left optic nerve was visualized and completely removed. The tumor extended about 6 mm. intracranially through the left optic foramen.

Convalescence from operation was uneventful, and the patient was dismissed from the hospital on the 11th postoperative day (Fig. 1). A letter from the patient's mother and a photograph of the patient (Fig. 2) received in the spring of 1954, about 12 years after the operative intervention, indicated that the patient was in good health.

Case 2.—A 2-year-old white girl was brought to the clinic because the parents were worried about her apparent loss of vision and prominence of the right eye. The parents stated that they first noticed the abnormality of the right eye about three months previous to coming to the clinic, and that the eye appeared to be turned to one side. Sometimes it would turn inward and sometimes outward. During the three months the child had complained occasionally that her eye hurt and she acted as though something were in it. Three weeks prior to her admission the parents took the child to their local ophthalmologist, and he suggested that she be taken to a larger clinic.

The results of general examination were unremarkable except as they related to the eye. The blood pressure was 110 mm. of mercury systolic and 70 mm. diastolic; the pulse rate was 84 beats per minute, and the temperature and respirations were normal. Examination of the eyes showed the tactile tension to be normal. The exophthalmometer reading, with base line at 86, was 19 mm. right eye and 17 mm. left eye. Palpation of the orbits did not give evidence of a tumor. The right eye was slightly divergent, and the right superior rectus muscle showed paresis, Grade 1 to 2. The eyelids, lacrimal apparatus, and conjunctivas were normal. The corneas were clear, and the anterior chambers were of normal depth. The pupils were round, equal, and 3 mm. in diameter. The right pupil did not react directly to light but reacted

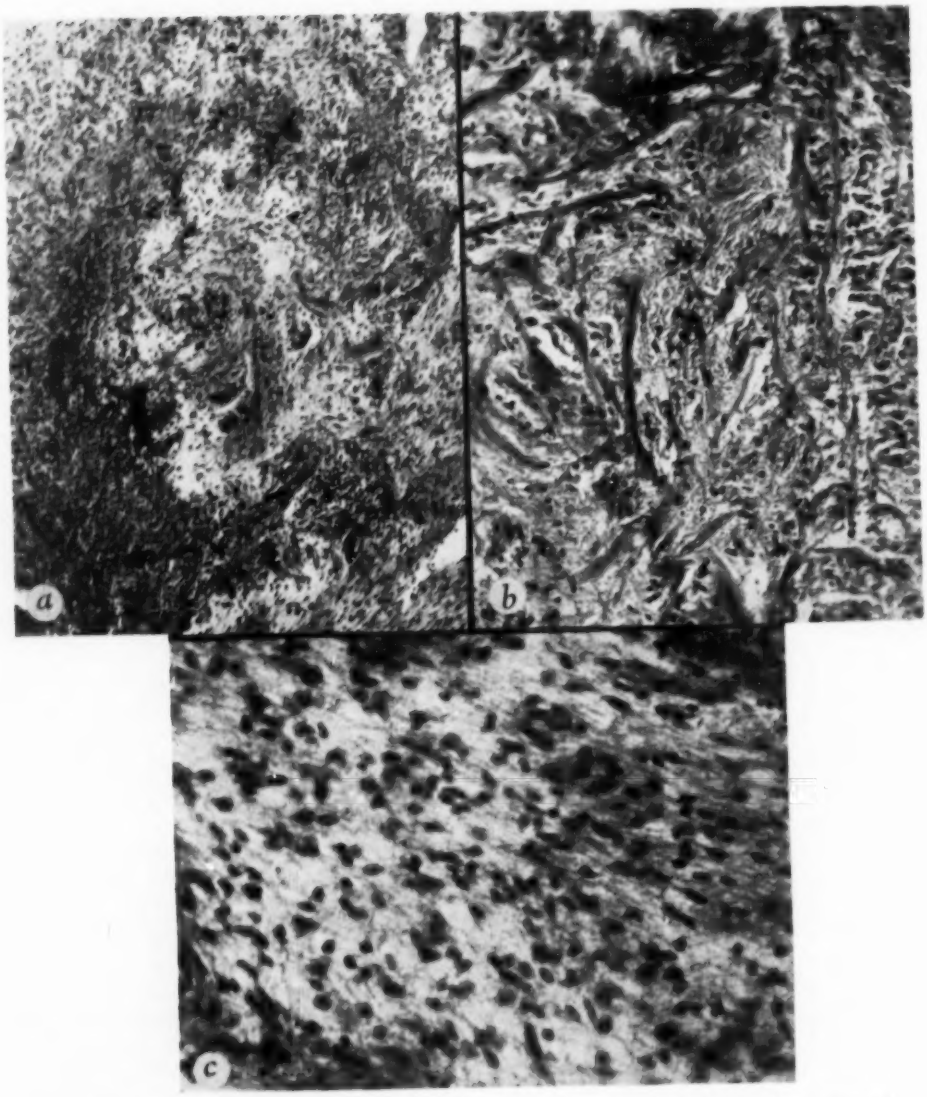


Fig. 1.—Microscopic section of typical astrocytoma (glioma) of the optic nerves, as described in reported cases. Hematoxylin and eosin stain. (*a*) ×100; (*b*) ×200; (*c*) ×300.

consensually to light and in accommodation. The pupil of the left eye reacted directly both to light and in accommodation. Examination of the optic fundi showed them to be essentially unremarkable except for the exceeding paleness of the optic disc on the right.

Routine laboratory studies showed the value for hemoglobin to be 10.9 gm. per 100 cc. of blood; the erythrocytes numbered 3,680,000, and the leucocytes 5,900, per cubic millimeter of blood, with a normal differential count. The results of urinalysis were within normal limits. Results of tests on blood serum were negative. Roentgenograms of the skull and special views of the orbits did not show evidence of any abnormality.

A diagnosis of intraorbital tumor on the right was made, and transcranial removal was advised and carried out. An intraorbital and intracranial tumor of the right optic nerve was encountered and completely removed. The optic nerve was divided

Fig. 2 (Case 1).—Appearance of the left eye in the photograph taken in the spring of 1954. The patient underwent operation on July 4, 1942.

just anterior to the chiasm and immediately behind the optic globe. The tumor was included between the two portions. Pathologically this tumor proved to be a fibrous astrocytoma.

The patient's convalescence was uneventful, and she was dismissed from the hospital on the eighth day after operation. She was seen again in November, 1947, approximately four months after operation, for a recheck examination, when the parents stated that she was unable to close the right eye completely. Examination showed ptosis of the right lid, exophthalmos, and partial immobility of the eyeball. The globe could be pressed deeply into the orbit without pain. The media was clear, and exophthalmoscopic examination showed an atrophic nerve head with pigmentary changes about the disc margins, characteristic of a nerve evulsion (Fig. 3).

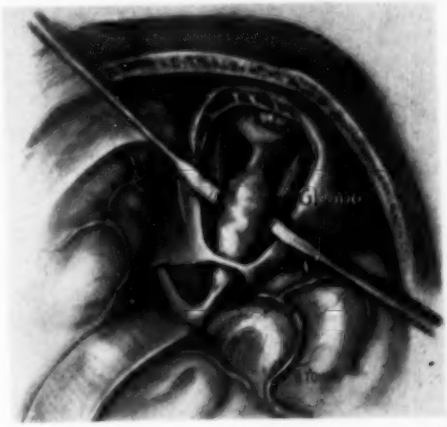
Case 3.—A 4½-year-old white boy was first seen at the clinic in April, 1953, with a main complaint of inability to see from the right eye. In January, 1953, the parents had noted a turning of the eye to one side, but they did not pay much attention to it. In March, 1953, the child said he was unable to see from his right eye, and examination of his eye at that time by his home physician revealed that he was blind in the right eye and that the muscles of that eye were considerably weakened. The child was hospitalized, and analysis of the cerebrospinal fluid revealed a concentration of protein of 55 mg. per 100 cc. At that time the child began to have headaches. He never complained of double vision, however.

The results of general examination were unremarkable except as they related to the eyes. The blood pressure, pulse, respiration, and temperature were recorded as normal. At 9 months of age the child had had a temperature of 102 F and a diagnosis of poliomyelitis had been made. Since the left foot turned in, the patient was put in a cast. In addition, the child was suspected of having had bronchial asthma. Other than this, the history was normal, except for the usual childhood diseases. The results of neurologic examination were essentially within normal limits, and the left eye was normal in all respects; the right eye showed convergent strabismus and slight proptosis. The pupil was fixed to light but reacted to consensual testing. The optic disc showed pallor, Grade 2, and the superior and inferior poles were elevated approximately 1 to 2 D. The veins appeared full, dark, and tortuous, and the impression was that the patient was harboring a tumor of the right optic nerve, presumably a glioma (low-grade astrocytoma).

Transcranial removal, approach to the nerve, and removal of the tumor were advised and carried out in April, 1953. A large dumbbell-shaped astrocytoma was encountered, involving the orbit and the intracranial portion of the nerve up to the sella turcica. The tumor was completely removed along with portions of the optic nerve.

The patient's postoperative convalescence was essentially uncomplicated, and he was dismissed from the hospital on the 11th day after operation.

Fig. 3.—Drawing of right optic nerve glioma as encountered at operation and as visualized by the neurosurgeon.



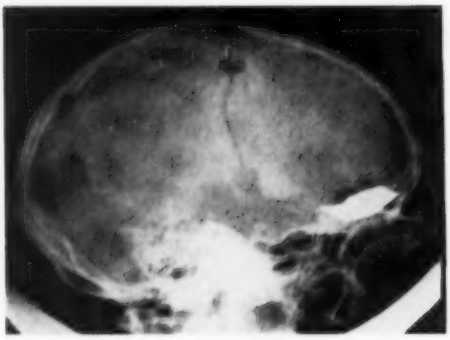


Fig. 4 (Case 3).—Stainless-steel cranioplasty to cover the orbit.

At the time of operation, stainless-steel cranioplasty was carried out over the orbit (Fig. 4).

A report from the home physician in April, 1954, approximately a year after operation, indicated that the boy's convalescence was satisfactory and he was leading a normal life. A photograph of the patient was obtained to show the condition of his right eye (Fig. 5).

Case 4.—A 13-year-old white boy was first seen at the clinic in January, 1944. On admission it was stated that a little more than a year prior to his registration at the clinic the patient had noted that his right eye was becoming more prominent than his left. This condition had gradually progressed until the time of his admission; however, he had no associated complaints. The boy's general health had remained excellent. His history was unremarkable, and his family history was not contributory.

General examination at the clinic was unremarkable except as it related to the patient's eyes. The blood pressure was 130 mm. of mercury systolic and 80 mm. diastolic; the pulse rate was 88 beats per minute, and the temperature and respirations were normal. Detailed examination of the eyes showed marked exophthalmos on the right. The exophthalmometer readings, with base line at 86, measured 28 mm. on the right and 19 mm. on the left. The lids of the right eye would not close completely, there being approximately a 4 mm. cleft when they were in the closed position. The lid margins were somewhat reddened. The pupils were equal in size and moderately dilated. The left pupil reacted normally to light and in accommodation, but the right pupil was sluggish in its reaction to light.

Fig. 5 (Case 3).—Appearance of the patient's right eye approximately 18 months after operation.

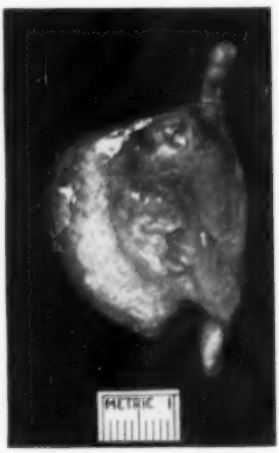


Fig. 6 (Case 4).—Gross specimen of a typical glioma of the optic nerve.

Consensual light reaction appeared normal bilaterally. Tension of the right eye appeared increased; the left eye was soft. The field of the left eye was roughly full, but it was impossible to test on the right side because of the poor vision. The extraocular movements were recorded as normal. The fundus of the right eye showed wrinkling of the retina in regions above the macula. The disc was pale, white, sharply outlined, and smaller than the left. The fundus of the left eye was recorded as normal. Examination of the visual fields showed right inferior altitudinal anopsia; the left was normal. Vision was 6/12 and 14/14 on the left, and the patient was able only to count fingers on the right.

The diagnosis of intraorbital tumor was made, and operation was carried out through the trans-

Fig. 7 (Case 4).—Eyes of patient approximately two and one-half years after operation.

cranial approach. An astrocytoma involving the optic nerve was encountered and removed. The tumor extended both intraorbitally and intracranially, from anterior to the optic chiasm to within 2 to 3 mm. of the posterior portion of the optic globe. It was completely removed (Fig. 6). After operation the patient had a little difficulty with breathing, and on bronchoscopy a fibrinous plug was removed from the trachea. Thereafter his convalescence was uneventful, and he was dismissed from the hospital on the 14th day after his operation. Reexamination in August, 1953, or nine years after operation, did not reveal further change in the appearance of his eye. The right globe pulsated and was divergent. The vision was nil (Fig. 7).

As a result of our experience with optic nerve gliomas, which will be reported more fully at another time, we suggest that all patients suspected of harboring a tumor affecting the optic nerve should be given the benefit of exploration, and that radical removal of the offending tumor should be carried out in those cases in which it is feasible. Knowledge of the pathologic processes has made us extremely reluctant to advise removal of the ocular globe or orbital exenteration, since it may be possible to retain the eyeball and oculomotor function, and thus have a better cosmetic result.

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Experimental Ocular Effects of High-Voltage Radiation from the Betatron

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The literature abounds with articles on the effects of ionizing radiation on the eye, beginning with Chalupecky [1] in 1897, two years after Roentgen's discovery of x-rays. The present report is concerned with an investigation employing the 20,000,000 volt betatron by Kerst and co-workers,* of the University of Illinois. This apparatus possesses distinct advantages in the study of radiobiologic changes in the animal eye. It is capable of producing either an x-ray or an electron beam with depth-dose curves quite different than those for lower-voltage machines.

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From the Department of Ophthalmology of the University of Illinois College of Medicine. This study was made under a grant from the U. S. Public Health Service.

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MATERIALS AND METHODS

For this study, 17 and 19 mev electrons and 23 mev x-rays were used. Figure 1 depicts the depth-dose curve for the 17 mev electron beam, showing that the surface dose is nearly maximum and remains so for the first 3 or 4 cm. Figure 2 gives the depth-dose curve for 25 mev x-rays, demonstrating the relatively low surface dosage and the slow decline after subsurface peak. Figure 3 illustrates the effect of increasing the voltage on the depth-dose curve for the electron beam. Figure 4 presents the isodose curves for the electron beam, and Figure 5, those for the x-ray beam.

It is evident that with the betatron x-ray beam an eye can be given high-dosage radiation to its posterior segment with relatively low dosage to its anterior segment. Furthermore, the eye can be placed at the peak of the curve, so that nearly maximum dosage may be delivered to all depths of the eye. The latter alternative was used in the present study. This was accomplished for the x-ray beam by placing a block of Lucite 3.4 cm. in thickness between the exit portal of the machine and the eye to be irradiated, and for the electron beam by

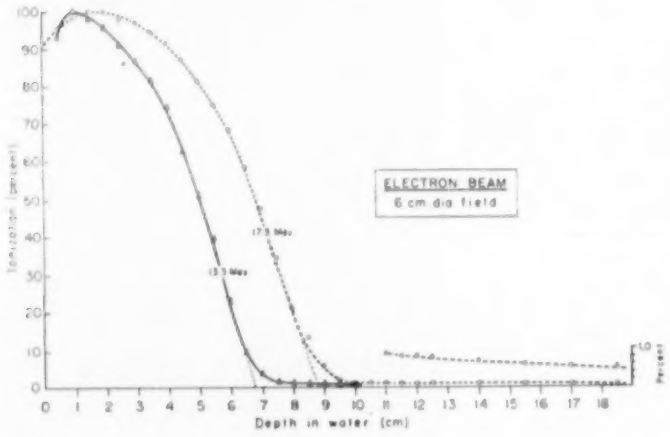


Fig. 1.—Depth-dose distribution in water along the central axis of the high-energy electron beam. Measurements made with a small ionization chamber in water. The dashed line beginning at a depth of 11 cm. represents *Brehmstrahlung*. The sensitivity of the amplifier was increased by a factor of 10 in this region. From Laughlin, J. S., and others: Some Physical Aspects of Electron Beam Therapy, Radiology **60**:165, 1953; published by the Radiological Society of North America.

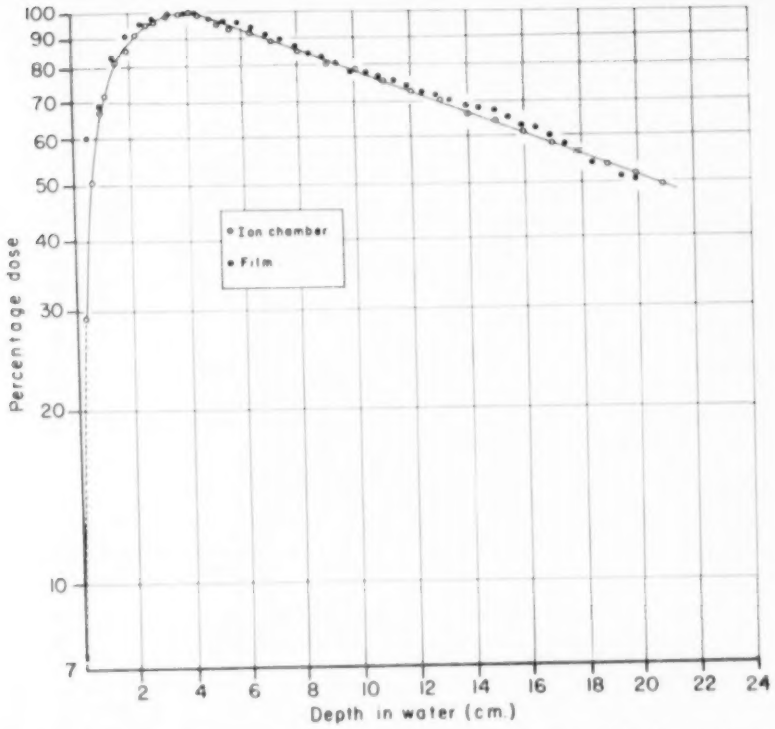


Fig. 2.—Depth-dose measurements for 25 mev x rays obtained with ionization chambers and with films in a water phantom. 25 cm. diameter field size. From Laughlin, J. S., and others: Dose Distribution Measurements with the University of Illinois 25 Mev. Medical Betatron, Am. J. Roentgenol. **65**:787, 1951; published by Charles C Thomas, Publisher, Springfield, Ill.

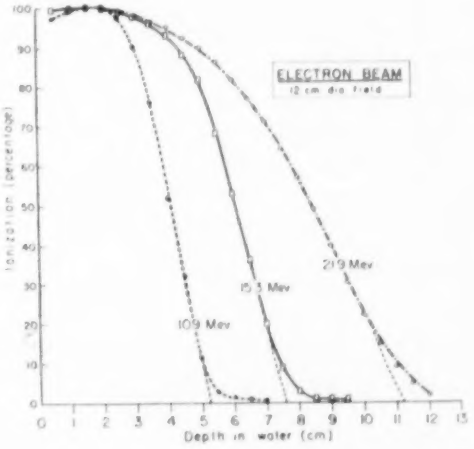


Fig. 3.—Depth-dose distributions in water along central axis of high-energy electron beam. Measurements were made with a small ionization chamber. From Laughlin, J. S., and others: Some Physical Aspects of Electron Beam Therapy, Radiology **60**:165, 1953; published by the Radiological Society of North America.

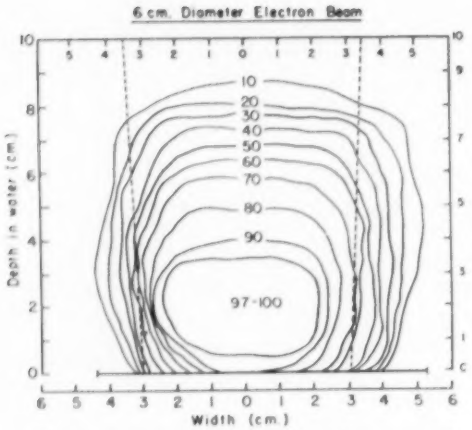


Fig. 4.—Isodose contours obtained in water with high-energy electron beam of 6 cm. Ionization was measured at points 1 cm. apart, and isodose contours were obtained by interpolation. Scattering material was employed to produce a uniform beam. From Laughlin, J. S., and others: Some Physical Aspects of Electron Beam Therapy, Radiology **60**:165, 1953; published by the Radiological Society of North America.

using no phantom. Portal diameters of 1.5 and 6.5 cm. were used for the electron beam, and of 1.5 and 2.5 cm. for the x-ray beam.

Nonalbino rabbits between the ages of 3 and 6 months were anesthetized intravenously with pentobarbital sodium, 25 mg/kg., and placed in a holder especially constructed to minimize movement and reduce discomfort. The right eye was aligned axially with the exit tube of the betatron. Single doses of either electrons or x-rays, ranging from 100 to 4500 r, were given. The eyes were studied at regular intervals with the slit-lamp microscope and ophthalmoscope. Some rabbits were followed as long as the health of the animal permitted or until a complete cataract developed. They were then killed with a large dose of pentobarbital sodium intravenously. The eyes were enucleated immediately and fixed in Zenker's and formalin solution. Specially large sagittal calottes, including the lens, were made in order to facilitate penetration of the celloidin into the lens. Other rabbits were used for special chronologic studies for 1650 and 250 r with the 2.5 cm. portal x-ray beam. Sections stained with hematoxylin and eosin were made at the time intervals indicated in the Table.

In some rabbits intraocular pressure estimations were made just prior to irradiation and at four months afterward. Ten minutes after receiving their pentobarbital intravenously for anesthesia, tetracaine hydrochloride, 0.5% solution, was instilled and the tensions were taken in each eye with the Schiøtz tonometer. The desirability of intravenous anesthesia in rabbits for tonometry was shown in a

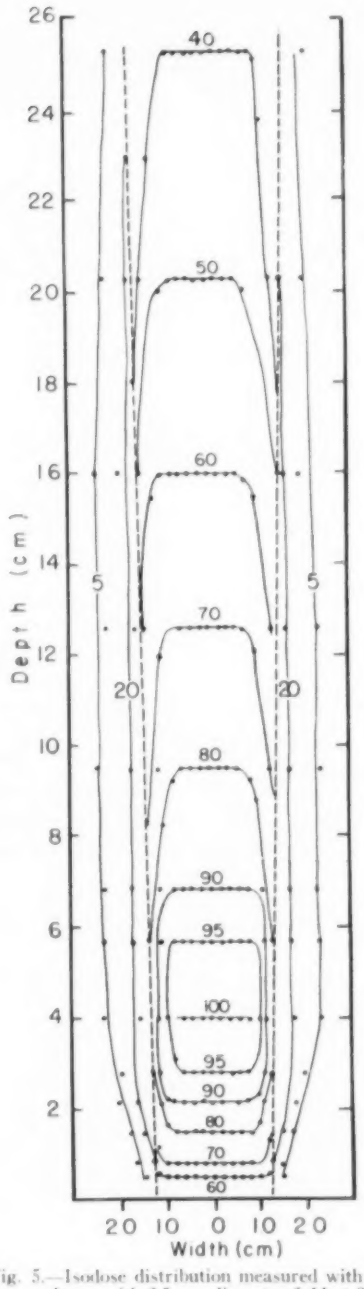


Fig. 5.—Isodose distribution measured with films for x-ray beam with 2.5 cm. diameter field at 80 cm. skin-target distance. From Laughlin, J. S., and others: Dose Distribution Measurements with the University of Illinois 25 Mev. Medical Betatron, Am. J. Roentgenol. **65**:787, 1951; published by Charles C Thomas, Publisher, Springfield, Ill.

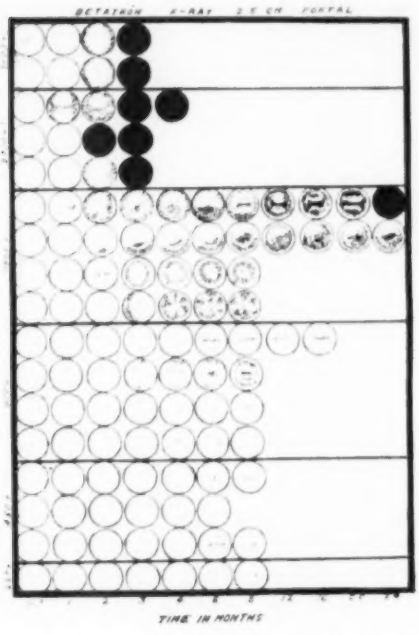


Chart 1.—Diagram of progression of clinical lens changes for betatron x-rays; 2.5 cm. portal.

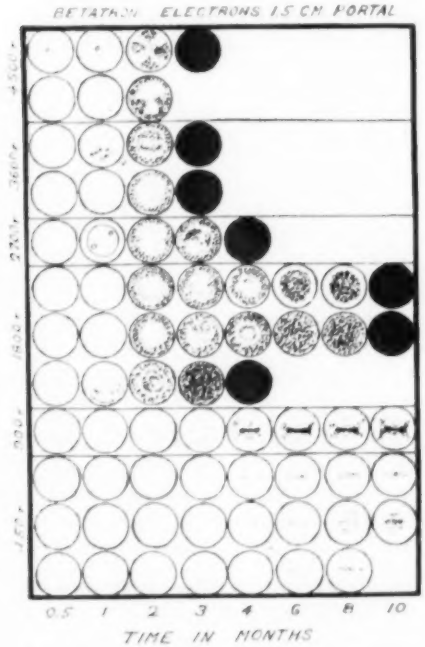


Chart 2.—Diagram of progression of clinical lens changes for betatron electrons,; 1.5 cm. portal.

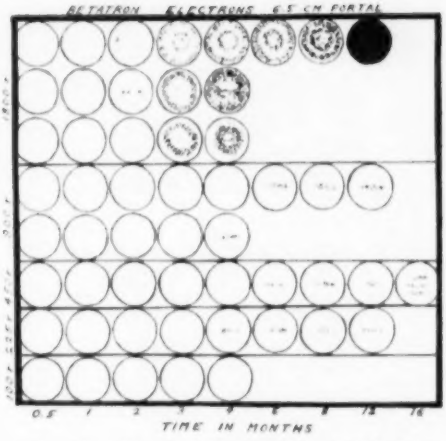


Chart 3.—Diagram of progression of clinical lens changes for betatron electrons; 6.5 cm. portal.

separate, unpublished, study. The variability of the readings in 96 eyes of rabbits which had been given pentobarbital anesthesia and topical tetracaine was compared with the variability of the readings in the eyes of 96 other rabbits which had received the tetracaine only. By computing the variation from the mean and analyzing by means of "Student's *t*-test," [7] the reliability was found to be significantly greater for the anesthetized group ($p < 0.01$). In order to increase accuracy, the average of three readings obtained alternately between the right and left eyes at very minute intervals was used to obtain each value in the above comparison. This method might be criticized because of the possible "massage

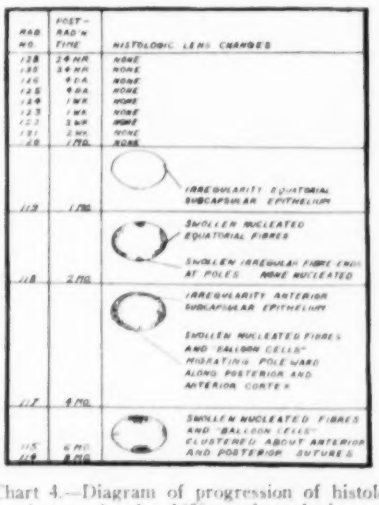

RAB NO.
POST-RADN TIME
HISTOLOGIC LENS CHANGES
NONE
IRREGULARITY EQUATORIAL SUBCAPSULAR EPITHELIUM
SWOLLEN NUCLEATED EQUATORIAL FIBRES
SWOLLEN IRREGULAR FIBRE ENDS AT POLES NONE NUCLEATED
IRREGULARITY ANTERIOR SUBCAPSULAR EPITHELIUM
SWOLLEN NUCLEATED FIBRES AND "BALLOON CELLS" MIGRATING POLEWARD ALONG POSTERIOR AND ANTERIOR CORTEX
SWOLLEN NUCLEATED FIBRES AND "BALLOON CELLS" CLUSTERED ABOUT ANTERIOR AND POSTERIOR SUTURES

Chart 4.—Diagram of progression of histologic lens changes in the 1650 r chronologic series; betatron x-rays; 2.5 cm. portal.

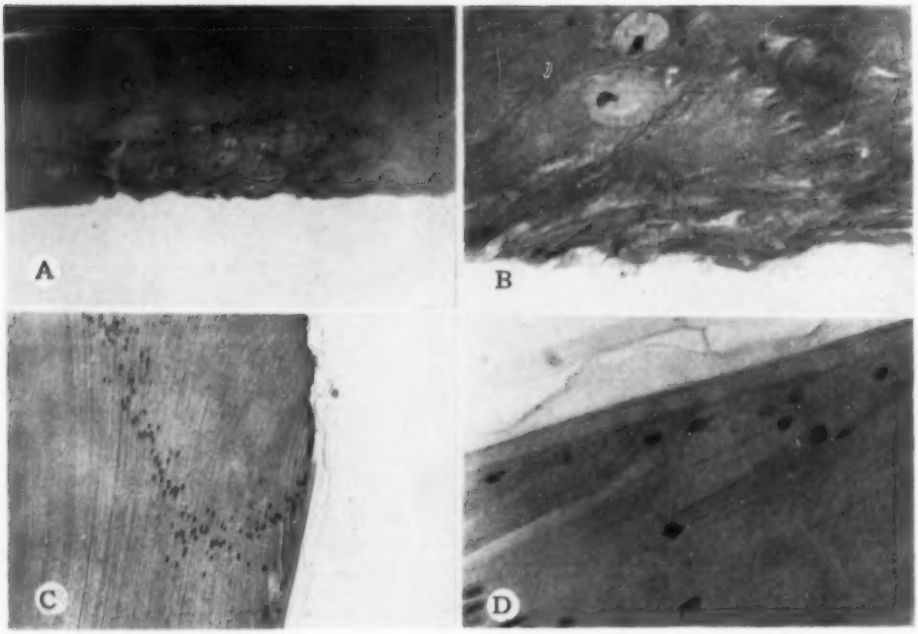


Fig. 6.—*A*, swollen fiber-ends and balloon cells about the posterior suture. Rabbit #59; 900 r electrons; 6.5 cm. portal; 4.0 months.

B, high-power magnification of *A*.

C, irregular equatorial fibers and nuclei. Rabbit #119; 1650 r x-rays; 2.5 cm. portal; 1.0 month.

D, high-power magnification of *C*.

effect" of three successive tonometric applications, but statistical analysis revealed no significant difference between the first and the third reading ($p > 0.6$).

RESULTS

For analysis of lesions, only the right eyes were used, although similar, but less intense, effects were noted in the left eyes. Rabbits receiving doses of 2700 r or more with the 6.5 cm. portal did not survive long enough for adequate study of the ocular effects.

Clinical Changes in Lens.—The cataractous changes noted in vivo are depicted diagrammatically in Charts 1, 2, and 3. These Charts indicate that the speed of onset and the intensity of the cataracts are roughly proportional to the dosage. With low doses (225 to 900 r) the first lens changes usually noted after three to six months were tiny, punctate opacities grouped about the posterior horizontal suture. They appeared as dark spots with the ophthalmoscope and as white dots with the slit-lamp microscope. Equatorial vacuoles were noted rarely in this dosage range. With doses of 1800 r, the initial changes after one to three months were usually equatorial, although occasionally vacuoles were first detected in the posterior cortex. They appeared as dark bubbles by ophthalmoscopy and as white spheres by direct slit-lamp illumination. With the passage of months these vacuoles increased in number and frequently appeared to migrate toward the posterior horizontal suture. Occasionally vacuoles seemed to migrate toward the anterior pole. Anterior subcapsular and anterior cortical haze and a paraxial ring of posterior cortical vacuoles occurred frequently with further progression of the cataract. Mature cataracts developed in some eyes given 1800 r after four months or more. With

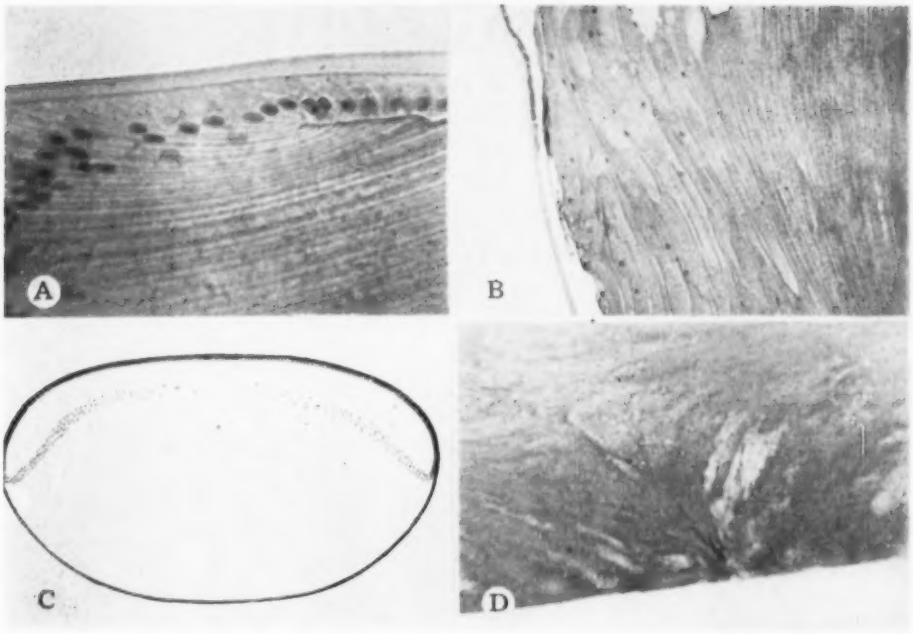


Fig. 7.—*A*, normal rabbit equatorial lens fibers.

B, swollen nucleated equatorial lens fibers. Rabbit #118; 1650 r x-rays; 2.5 cm. portal; 2.0 months.

C, diagram of normal rabbit lens nuclear bow.

D, swollen fiber-ends at posterior suture. Rabbit #118; 1650 r x-rays; 2.5 cm. portal; 2.0 months.

higher doses similar, but more rapid, changes occurred.

Histologic Changes in Lens.—The above-mentioned tiny, punctate opacities about the posterior horizontal suture, representing the first clinically recognizable lens change in low-dosage irradiation, coincided histologically with the appearance of balloon cells and swollen fiber ends. The balloon cells (Fig. 6*A* and *B*) are large round or oval cells with pale-staining, slightly granular cytoplasm. They usually contain one, and occasionally more than one, nucleus. The swollen ends of fibers (Fig. 7*D*) contain a pale-staining cytoplasm and irregular and vague cell boundaries.

For the intermediate dose of 1650 r, the progress of the histologic lens changes is summarized diagrammatically in Chart 4. At one month there was slight irregularity of the equatorial subcapsular epithelium and a few slightly swollen equatorial fibers (Fig. 6*C* and *D*). These changes may be compared with the equator of the normal lens in Figure 7*A*. At two months there were marked swelling and derangement of the equatorial cortical lens fibers with poleward migration of swollen nucleated fibers (Fig. 7*B*). This resulted in disruption of the pattern of nuclei in the lens bow (Figure 7*C* is a diagram of the normal rabbit lens bow). Swellings and irregularity of staining properties of the fiber ends were noted in the regions of the anterior and posterior sutures (Fig. 7*D*). At four months the anterior subcapsular epithelium presented irregularity and sparsity of nuclei (Fig. 8*A*). Balloon cells had spread further toward the poles, and swollen nucleated fibers were scattered along the posterior cortex (Fig. 8*B* and *C*). At six and eight months

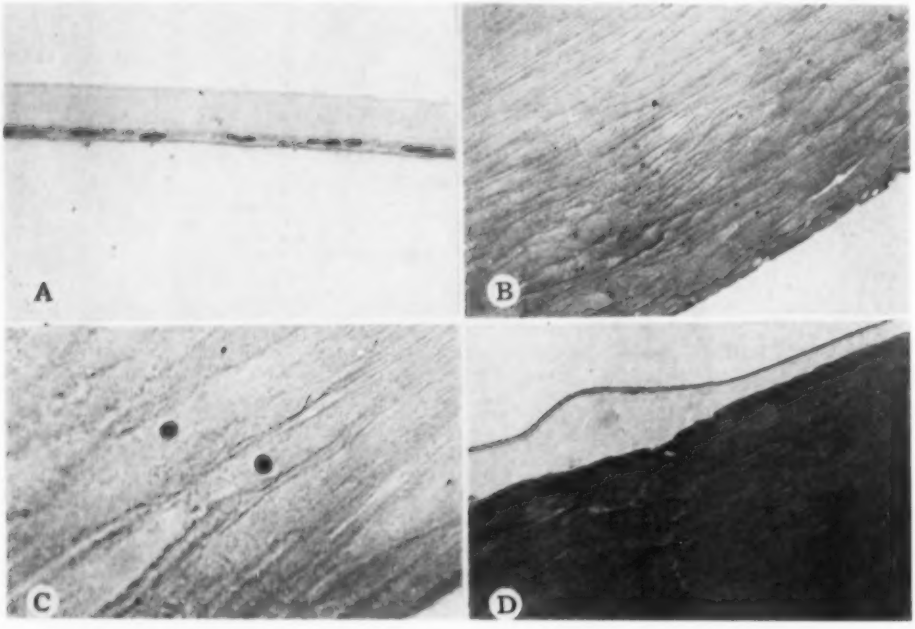


Fig. 8.—*A*, irregularity and sparsity of nuclei of anterior subcapsular epithelium. Rabbit #117; 1650 r x-rays; 2.5 cm. portal, 4.0 months.

B, swollen nucleated fibers in posterior cortex. Rabbit #117; 1650 r x-rays; 2.5 cm. portal; 4.0 months.

C, high-power view of *B*.

D, balloon cells and swollen fibers about anterior suture. Rabbit #115; 1650 r x-rays; 2.5 cm. portal; 6.0 months.

swollen nucleated fibers and balloon cells were clustered more densely about the anterior (Fig. 8*D*) and posterior sutures.

In more advanced cataracts resulting from higher doses (1800-4500 r) the following effects were noted: breakdown of portions of the cortical architecture to pink amorphous material (Fig. 9*A* and *B*); vacuolar changes in the anterior subcapsular epithelium (Fig. 9*C*); thinning of the anterior subcapsular epithelium in some instances to such extent that it presented only a fine membrane, with intermittent thickenings representing the nuclear remnants (Fig. 9*D*), and breakdown of the fibrous architecture of the lens nucleus to pink amorphous material (Fig. 10*A*). Structure of the normal rabbit lens nucleus is seen in Figure 10*B*.

Our lens sections were all sagittal and therefore did not reveal the early cytologic changes in the anterior subcapsular epithelium noted by other workers using flat preparations.

Clinical Changes in Cornea.—The slit-lamp microscope revealed no corneal lesions after doses of 900 r or less. With doses of 1800 and 2700 r, the initial corneal change after two to four weeks was a fine superficial punctate haze interspersed with fine brown pigment granules, which appeared to have migrated from the limbus. With the passage of months these tended to group near the center of the cornea. With doses of 3600 and 4500 r, the superficial changes were similar to those for the intermediate doses; but, in addition, marked corneal swelling, presenting a striking "ground glass" appearance and anterior stromal vascularization, occurred frequently after one to two months.

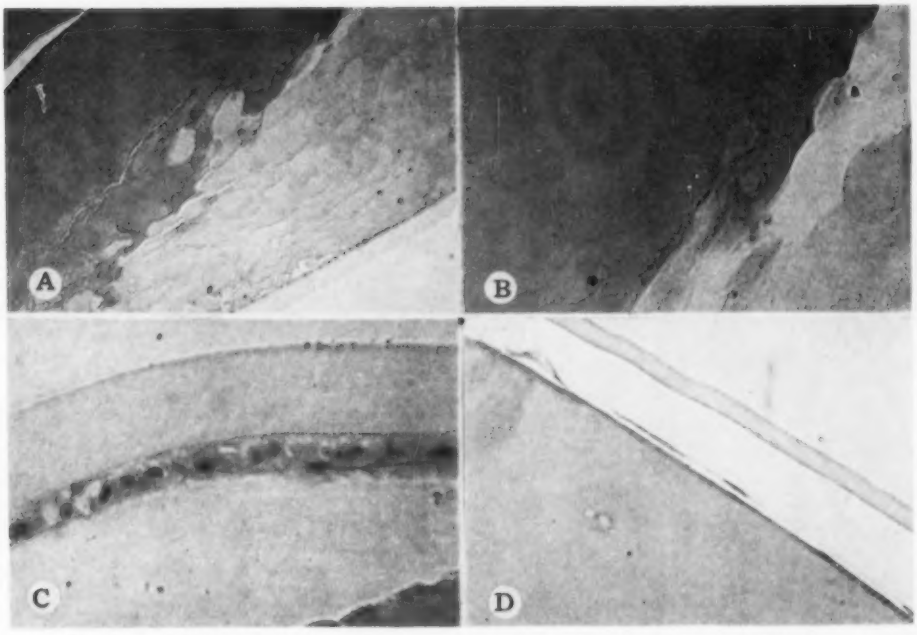
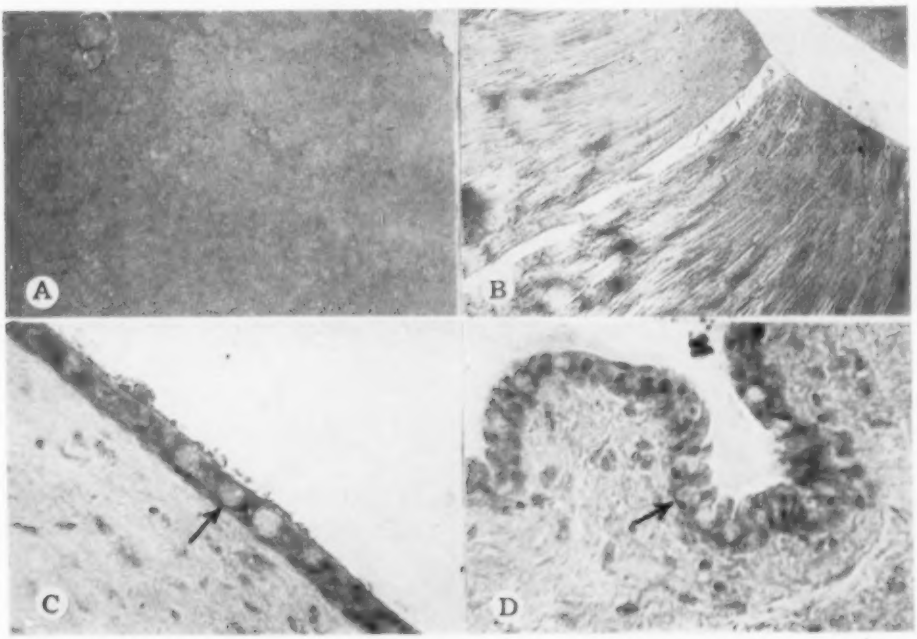


Fig. 9.—*A*, breakdown of cortical architecture to amorphous material. Rabbit #76; 1800 r electrons; 1.5 cm. portal; 4.0 months.
B, high-power view of *A*.
C, vacuolar changes in anterior subcapsular epithelium. Rabbit #76; 1800 r electrons; 1.5 cm. portal; 4.0 months.
D, thinning of anterior subcapsular epithelium to a fine membrane. Rabbit #88; 3600 r x-rays; 2.5 cm. portal; 3.0 months.

Fig. 10.—*A*, breakdown of lens nucleus architecture to amorphous material. Rabbit #89; 2700 r x-rays; 2.5 cm. portal; 3.0 months.
B, normal rabbit lens nuclear architecture.
C, corneal epithelial thinning and vesiculation. Rabbit #69; 4500 r electrons; 1.5 cm. portal; 3.0 months.
D, goblet cells of normal rabbit bulbar conjunctiva.



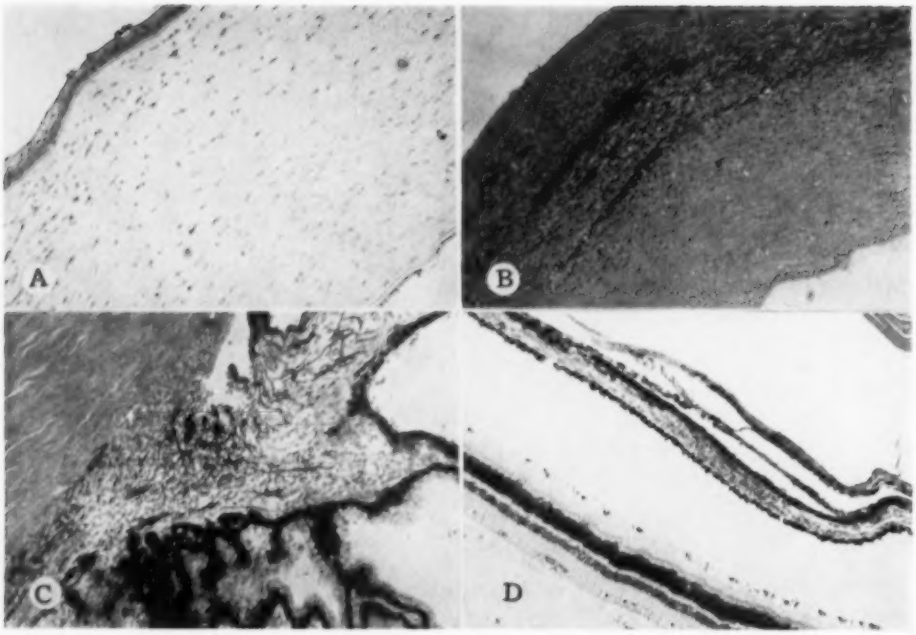


Fig. 11.—*A*, edema of anterior corneal stroma. Rabbit #87; 3600 r x-rays; 2.5 cm. portal; 3.0 months. *B*, stromal cellular infiltration and neovascularization. Rabbit #68; 4500 r electrons; 1.5 cm. portal; 3.0 months.

C, cellular infiltration and vascular congestion in ciliary body. Rabbit #128; 1650 r x-rays; 2.5 cm. portal; 24 hours.

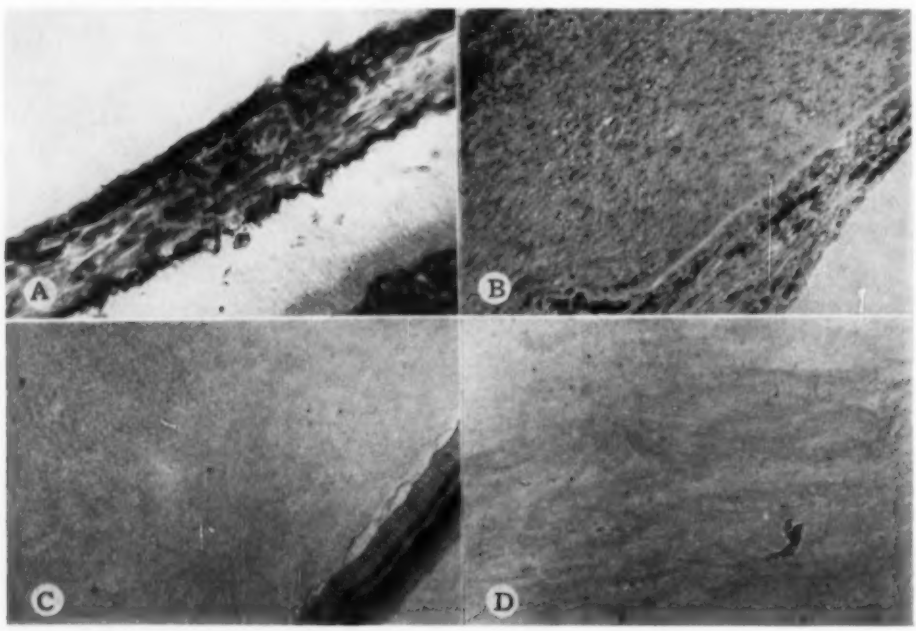
D, cellular infiltration in the choroid. Rabbit #128; 1650 r x-rays; 2.5 cm. portal; 24 hours.

Fig. 12.—*A*, high-power magnification of choroid from same eye as that in Figure 11*D*.

B, circumcorneal inflammatory change and peripheral anterior synechia. Rabbit #87; 3600 r x-rays; 2.5 cm. portal; 3.0 months.

C, granular material in vitreous. Rabbit #88; 3600 r x-rays; 2.5 cm. portal; 3.0 months.

D, fibrillar pattern of normal rabbit vitreous.



Histologic Changes in Cornea.—The histologic findings in the cornea are summarized in the Table. The superficial haze observed clinically could be explained histologically by subepithelial cellular infiltration and by roughening, thinning, and vesiculation of the epithelium (Fig. 10*C*). The vesiculated cell has a pale-staining cytoplasm with an eccentric nucleus and resembles surprisingly the goblet cell of the normal rabbit conjunctiva (Fig. 10*D*). It is conceivable that conjunctival cells might have migrated onto a damaged cornea, or that this vesiculated cell is an altered corneal epithelial cell. The corneal swelling and "ground glass" appearance seen with the slit lamp correspond histologically with edema of the anterior half of the stroma (Fig. 11*A*). Also, cellular infiltration of the stroma and neovascularization were evident after higher doses (Fig. 11*B*).

Clinical Inflammatory Changes.—The eyes were not examined clinically during the first week; hence the early phase of uveitis noted below was not observed until pathologic sections were obtained. The Tyndall phenomenon in the aqueous was seen rarely with 1800 r, and was usually present in doses of 2700 r or more at two to three months after irradiation. Circumcorneal hyperemia was noted frequently with doses of 1800 r at one month and persisted in many cases, particularly in the higher doses, as long as the rabbit was observed.

Histologic Inflammatory Changes.—For purposes of convenience, congestion and cellular infiltration in the circumcorneal area are listed with uveal changes in the Table. As early as 24 hours after irradiation with 1650 r of x-rays, there appeared polymorphonuclear- and round-cell infiltration and vascular congestion in the ciliary body (Fig. 11*C*) and choroid (Figs. 11*D* and 12*A*), faint coagulum in the anterior chamber, and cellular infiltration in the circumcorneal area. This initial uveitis subsided within one week and did not recur within the eight-month follow-up period. Higher doses produced coagulum and cells in the anterior chamber, peripheral anterior synechiae, and circumcorneal inflammatory change at three to four months after irradiation (Fig. 12*B*).

Vitreous.—Radiational change of the vitreous was not observed ophthalmoscopically, but, after doses of 1800 r or more, histologic examination revealed conversion of the normal faint fibrillar architecture (Fig. 12*D*) to a dense pink granular material (Fig. 12*C*; Table).

Retina.—Slight change in the periphery of the retina was noted in some of the sections three months after irradiation with 3600 and 4500 r. This consisted of atrophy in the bacillary layer in the vicinity of the ora serrata. There was no change in the appearance of the retina in vivo at two weeks or later.

Optic Nerve and Sclera.—Our study failed to reveal radiational change in these structures.

Conjunctival Hyperemia.—This was a common early finding after irradiation, even with low doses. It is somewhat unreliable as an early sign of radiational effect in the rabbit, since it occurs frequently in the unirradiated eye as a result of minor irritants. Circumcorneal hyperemia is described under uveal changes.

Epilation of the Lids.—Epilation was rarely noted in doses of 900 r or less but appeared in most rabbits given 1800 r or more at two weeks to three months after irradiation. It usually decreased gradually in intensity and area with the passage of months.

Ocular Tension.—High doses of radiation produced a slight lowering of tension. The average differences between three initial and three tonometric readings after four months on 18 eyes of nine rabbits in the high-dose range (1800 to 4500 r) and 12 eyes of six rabbits in the low-dose range (0 to 900 r) were compared and analyzed by the *t* test.[7] This revealed a small, but statistically significant (*p*-approximately 0.01) reduction of tension for the high doses.

COMMENT

High-voltage ionizing radiation produces changes in the rabbit eye similar to those described previously for lower voltages. We

Summary of Histologic Findings

	Rabbit No.	Dosage, r	Type of Radiation	Portal Size, Cm.	Postirradiation Time	Cornea: Epithelium: Thinning	Cornea: Epithelium: Vesiculation	Cornea: Anterior Stroma: Vascularization	Cornea: Anterior Stroma: Cellular Infiltration	Cornea: Anterior Stroma: Edema	Uvea: Congestion and Cellular Infiltration: Anterior Chamber Coagulum	Uvea: Congestion and Cellular Infiltration: Circumcorneal Area	Uvea: Congestion and Cellular Infiltration: Iris	Uvea: Congestion and Cellular Infiltration: Ciliary Body	Uvea: Congestion and Cellular Infiltration: Choroid	Granular Vitreous Degeneration	Lens Change	Retinal Change
	104	4500	X-ray	1.5	3.5 mo.	....	....	....	....	....	++++	++++	....	....	....	++++	++++	....
	68	4500	Elec.	1.5	3.0 mo.	+	+	++	++	++	....	++	....	....	....	++++	++++	±
	69	4500	Elec.	1.5	3.0 mo.	+	++	++	++	++	....	+++	....	....	....	....	++++	±
	88	3600	X-ray	2.5	3.0 mo.	+	....	....	+	....	++++	++	....	....	....	++++	++++	±
	87	3600	X-ray	2.5	3.0 mo.	+	....	....	++	++	++++	+++	±	....	....	++++	++++	+
	70	3600	Elec.	1.5	3.0 mo.	....	....	++	++	....	....	++++	....	....	....	++++	++++	....
	72	3600	Elec.	1.5	3.0 mo.	....	....	....	....	....	....	++	....	....	....	++++	++++	....
	89	2700	X-ray	2.5	3.0 mo.	++	++	....	+	+	....	+	....	....	....	++	++++	....
	90	2700	X-ray	2.5	3.0 mo.	++	++	....	+	....	++	++++	....	....	....	++++	++++	....
	73	2700	Elec.	1.5	2.0 wk.	....	....	....	....	....	....	....	....	....	....	....	....	....
	108	2700	X-ray	1.5	6.0 mo.	....	....	....	....	....	....	....	....	....	....	....	++	....
	5	1800	X-ray	2.5	20.0 mo.	....	....	....	....	....	++	±	....	....	....	++	++++	....
	35	1800	Elec.	6.5	18.0 mo.	....	....	....	....	....	....	+	....	....	....	....	+++	....
	56	1800	Elec.	6.5	4.0 mo.	....	....	....	....	....	....	+	....	....	....	....	++	....
	57	1800	Elec.	6.5	4.0 mo.	....	....	....	....	....	....	....	....	....	....	....	....	....
	67	1800	Elec.	6.5	10.0 mo.	....	....	....	....	....	....	+	....	....	....	++++	++++	....
	75	1800	Elec.	1.5	10.0 mo.	....	....	....	....	....	....	....	....	....	....	++	++++	....
	76	1800	Elec.	1.5	10.0 mo.	....	++	....	++	....	....	....	....	....	....	....	++++	....
Chronologic Series	114	1650	X-ray	2.5	8.0 mo.	....	....	....	....	....	....	....	....	....	....	....	++	....
	115	1650	X-ray	2.5	6.0 mo.	....	....	....	....	....	....	....	....	....	....	....	++	....
	117	1650	X-ray	2.5	4.0 mo.	....	....	....	....	....	....	....	....	....	....	....	++	....
	118	1650	X-ray	2.5	2.0 mo.	....	....	....	....	....	....	±	....	....	....	....	++	....
	119	1650	X-ray	2.5	1.0 mo.	....	....	....	....	....	....	....	....	....	....	....	±	....
	120	1650	X-ray	2.5	1.0 mo.	....	....	....	....	....	....	....	....	....	....	....	....	....
	121	1650	X-ray	2.5	2.0 wk.	....	....	....	....	....	....	....	....	....	....	....	....	....
	122	1650	X-ray	2.5	2.0 wk.	....	....	....	....	....	....	....	....	....	....	....	....	....
	123	1650	X-ray	2.5	1.0 wk.	....	....	....	....	....	....	....	....	....	....	....	....	....
	124	1650	X-ray	2.5	1.0 wk.	....	....	....	....	....	....	....	....	....	....	....	....	....
	125	1650	X-ray	2.5	4.0 days	....	....	....	....	....	....	....	....	±	....	....	....	....
	126	1650	X-ray	2.5	4.0 days	....	....	....	....	....	....	....	....	±	+	....	....	....
	135	1650	X-ray	2.5	24.0 hr.	....	....	....	....	....	++	+	±	++	+	....	....	....
	128	1650	X-ray	2.5	24.0 hr.	....	....	....	....	....	±	++	±	++	+	....	....	....
	59	900	Elec.	6.5	4.0 mo.	....	....	....	....	....	....	....	....	....	....	....	+	....
	55	900	Elec.	6.5	6.0 mo.	....	....	....	....	....	....	....	....	....	....	....	+	....
	51	700	X-ray	2.5	18.0 mo.	....	....	....	....	....	....	....	....	....	....	....	+	....
	38	450	Elec.	6.5	18.0 mo.	....	....	....	....	....	....	....	....	....	....	....	+	....
	33	450	Elec.	6.5	19.0 mo.	....	....	....	....	....	....	....	....	....	....	....	+	....
Chronologic Series	148	250	X-ray	2.5	6.0 mo.	....	....	....	....	....	....	....	....	....	....	....	....	....
	134	250	X-ray	2.5	4.0 mo.	....	....	....	....	....	....	....	....	....	....	....	....	....
	136	250	X-ray	2.5	1.0 mo.	....	....	....	....	....	....	....	....	....	....	....	....	....
	137	250	X-ray	2.5	1.0 mo.	....	....	....	....	....	....	....	....	....	....	....	....	....
	139	250	X-ray	2.5	2.0 wk.	....	....	....	....	....	....	....	....	....	....	....	....	....
	140	250	X-ray	2.5	1.0 wk.	....	....	....	....	....	....	....	....	....	....	....	....	....
	141	250	X-ray	2.5	1.0 wk.	....	....	....	....	....	....	....	....	....	....	....	....	....
	147	250	X-ray	2.5	5.0 days	....	....	....	....	....	....	....	....	....	....	....	....	....
	146	250	X-ray	2.5	5.0 days	....	....	....	....	....	....	....	....	....	....	....	....	....
	143	250	X-ray	2.5	24.0 hr.	....	....	....	....	....	....	....	....	....	....	....	....	....
	142	250	X-ray	2.5	24.0 hr.	....	....	....	....	....	....	....	....	....	....	....	....	....
	62	100	Elec.	6.5	4.0 mo.	....	....	....	....	....	....	....	....	....	....	....	....	....

feel, however, that the betatron provides an excellent means for studying the ocular effects of radiation because of the unique shape of the depth-dose curve, particularly that of the x-ray beam. By placing the eye at the peak of the curve, the dose in all portions of the globe can be maintained at maximum. If the eye is positioned at the start of the curve, changes in the posterior segment may be observed while relatively unobstructed by changes in the anterior segment.

No marked difference in ocular effects were noted for the electron and the x-ray beams. This experience has been reported by others.[8] Portal size (1.5, 2.5, and 6.5 cm.) also had no appreciable influence upon the results, except that with the 6.5 cm. portal doses of 2700 r and higher resulted in early death of the rabbit, preventing adequate cataract follow-up.

Our findings regarding the development of cataractous changes are for the most part in accord with those of previous workers in the field.† The clinical appearance of cortical vacuoles was usually accompanied by the histologic picture of balloon cells in our study, although the appearance of vacuoles might also be produced by cystic clefts, as noted by von Sallmann.‡ The balloon cells, called pseudoepithelial cells by Rohrschneider,[15] and *Blasenzellen* ("bladder cells") by Kruckman,[16] have been further described by Leinfelder and Kerr,[10] von Sallmann,[12] Cogan and Donaldson,[13] and Cogan, Donaldson, and Reese.[17] Our work supports the belief that they are derived from the developing equatorial fibers undergoing radiational change.[18] The chronologic studies described in the present report indicate that the nucleated balloon cells migrate from their site of origin at the equator to the anterior and posterior poles. The clinical progress of the vacuoles is of the same character. Therefore we believe that clinical vacuoles usually result from balloon cells rather than from intercellular hydration phenomena. Their migration seems most probably the result of their being crowded away from the equator by newly developed fibers, both normal and pathologic. Their tendency to group in the region of the sutures and at the poles is consistent with the latter hypothesis. Cogan and Donaldson [13] suggest that lowered tissue pressure in the region of the sutures may account for it. This concept is supported by their finding of vacuoles along the suture lines in freshly excised, unirradiated lenses which had been immersed in water.

Whether the fine, punctate opacities about the posterior horizontal suture seen clinically in low dosage consist of small balloon cells or swollen fiber ends or both is not certain. From a total of five eyes in our series receiving low-dosage radiation § with posterior sutural punctate opacities at four months, histologic section revealed swollen fiber ends in four and balloon cells about the posterior suture in all five. The more discrete boundary of the balloon cells, moreover, suggests that they give rise to the punctate opacities.

Swelling and degenerative changes in the equatorial subcapsular cells,‖ abnormality and attenuation of the anterior subcapsular epithelium,¶ atrophy of the anterior subcapsular epithelium to a fine membrane,[19] and destruction of the cortical architecture # have all been observed in previous studies. Our finding of breakdown of the structure of the lens nucleus in high doses suggests that intense radiation may exert a direct effect on the developed lens fibers, or that cortical, epithelial, or capsular changes may give rise to some secondary effect on the lens nucleus.*

Corneal haze in early clinical radiation change has been reported by numerous investigators. Superficial punctate opacification

† References 9 to 13.

‡ References 12 and 14.

§ Two of these were left eyes which had received small amounts of stray radiation from the portal centered for the right eye.

‖ References 10, 12, and 15 to 19.

¶ References 10, 15, 17, 18, 20, and 21.

References 17, 18, and 19.

* The view expressed by Stallard [22] and Milner [23] that radiational lens change is secondary to changes in the ciliary body was largely refuted by the experimental work of Goldmann and Liechti [11] and Alter and Leinfelder.[24]

was noted in particular by Jacoby,[25] and pigment migration, cellular infiltration, and thinning of the epithelium, by Rohrschneider.[15] Vesiculation of the epithelial cells was noted by Birch-Hirschfeld [26] and Jacoby,[25] but we could find no mention in the literature of their remarkable resemblance to the normal conjunctival goblet cells. Further studies might be made to determine whether they are altered corneal epithelial cells or conjunctival cells which had migrated onto the cornea, along with reparative limbal epithelial cells. It would also be of interest to know whether these cells possess secretory activity or not.

Our data indicate that after intermediate doses there is an early phase of uveitis, particularly in the ciliary body, beginning within the first 24 hours and subsiding within a week. Although we do not have sections within the first week for higher doses, it is assumed that the initial uveal inflammation would be more intense the higher the dosage. Another phase of inflammation was noted in doses of 2700 r or more after two months. This consisted of the clinical and histologic picture of coagulum in the anterior chamber and congestion and infiltration in the circumcorneal area. At this period corneal changes were prominent, but the ciliary body and choroid were relatively inactive. Therefore it is assumed that the anterior segment inflammation was largely a response to corneal damage. It may be inferred, then, that the irradiated rabbit eye shows two principal types of inflammatory response: The first is an immediate and transitory uveitis, and the second is a delayed keratitis with anterior segment inflammatory reaction.

Whether the fine pink-staining granular material noted in the vitreous in high doses is merely serous infiltration from inflammatory change, or whether it is a specific breakdown of the vitreous itself is not clear. There has been considerable controversy in the literature as to whether the retina and optic nerve are radiosensitive † or radioresistant.‡ There is recent evidence that the retina undergoes degenerative change with doses as low as 2,000 r.[27] Minimal atrophy of the bacillary layer in the retinal periphery was noted by us in doses of 3600 and 4500 r. No scleral lesions resulting from irradiation were seen in this study. Perhaps they would have been evident in longer follow-up periods.[28]

Although Aulamo [27] noted no change in intraocular pressure, our data indicate that slight hypotony occurs with higher doses after four months. Anesthetizing the rabbits and using statistical calculation were important in revealing this effect. The decreased tension was probably the result of the concurrent inflammation.

† References 25, 26, 29, 30, and 31.

‡ References 15, 32-34.

SUMMARY

A study of the clinical and histologic effects of irradiating the rabbit eye with 16-19 mev electrons and 23 mev x-rays by means of the betatron for a wide dosage range is described. The betatron is advantageous in studying ocular radiation changes because of its depth-dose characteristics. Nearly uniform dosage may be obtained throughout the eye; or, if so desired, the dose in the anterior segment may be made quite low relative to that in the posterior segment. For the present investigation, conditions were so arranged that the dose was approximately the same for all depths of the eye so that relative susceptibilities of various portions of the eye might be assessed.

Most of the ocular changes observed in this project are in agreement with those cited by other workers using lower-voltage radiation. Descriptions of changes in the cornea, lens, uvea, vitreous, and hair are presented. Posterior subcapsular opacities were noted clinically, and corresponding changes were noted histologically four to six months after doses as low as 225 r. The sequence of events in the morphology of cataract development after the first month following irradiation is described in detail. Cells resembling conjunctival goblet cells were noted in the corneal epithelium after high-dosage irradiation. Two phases of inflammation are described. The first is an early transient uveitis, after doses as low as 1650 r. The second is a delayed

keratitis with anterior segment inflammatory change, after doses of 2700 r or more. Granular change in the vitreous occurred after doses of 1800 r or more. A mild hypotony four months after high-dosage radiation was demonstrated with the aid of general anesthesia and biometric analysis. Slight change in the sensient layer of the peripheral retina was observed after higher doses. The sclera and optic nerve revealed no changes in this study, with use of ordinary histologic technique. Neither portal size nor type of beam (x-ray or electron) appears to influence the radiational effect of the betatron upon the rabbit eye.

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The Nature of Vergence Revealed by Electromyography

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In a previous publication innervational aspects of convergence and divergence revealed by electromyography were described (Breinin and Moldaver,[1] 1955). It was shown that patients with intermittent exotropia experienced active innervation of the lateral rectus on diverging from the near point of convergence and at all times when the nonfixing eye deviated outward. This was true for all fixation distances.

This report concerns additional data on the vergence mechanisms. In the cases of intermittent exotropia cited above, a remarkable finding in all instances was the fact that only the deviating eye showed increased innervation of the lateral rectus. The fixating eye showed no alteration of the innervation of either lateral or medial rectus. At first sight this suggested that the exo deviation was due to a monocular dissociation and that Hering's Law was invalid for this condition. If this were so, we should have to speak of an "abduction" rather than a "divergence" anomaly. Hering himself, however, has supplied the clue to the innervational mechanism of exo and eso deviations in his explanation of asymmetrical convergence.* He stated that convergence on a fixation point which lies on the fixation axis of one eye in the primary position (in contrast to midline convergence) can be analyzed into two movements. There is convergence of both eyes to the midline and then a version to the side of the fixation object. This is synthesized into a single movement such that the eye on the side of the fixation object does not move because its convergence is neutralized by the version. The other eye must execute twice as great a movement to maintain its fixation, and this movement is compounded of convergence augmented by version.

The truth of this dual movement can be demonstrated electromyographically. It has been previously shown that the medial and lateral recti are always innervationally active in the primary position (Breinin and Moldaver[1]; Fig. 1). In midline convergence both medial recti are increasingly innervated and both lateral recti correspondingly inhibited (Fig. 2). When the gaze is swung to one side, the medial rectus of the eye on that side exhibits a diminution of innervation, while that of the lateral rectus is increased (Fig. 3). The result for that eye is to restore the exact balance and level of innervation which existed prior to the convergence, and which it habitually exhibits in the primary position. The other eye shows a correspondingly greater level of innervation of the medial rectus and inhibition of the lateral rectus, called for by the greater excursion (Fig. 4).

When this experiment is repeated with the fixation object approximated on the axis of one eye, the result is identical. Indeed, it must be, for if the innervation of that eye were to change it would have to move, but fixation—a sensory essential—precludes such movement. The alternative,

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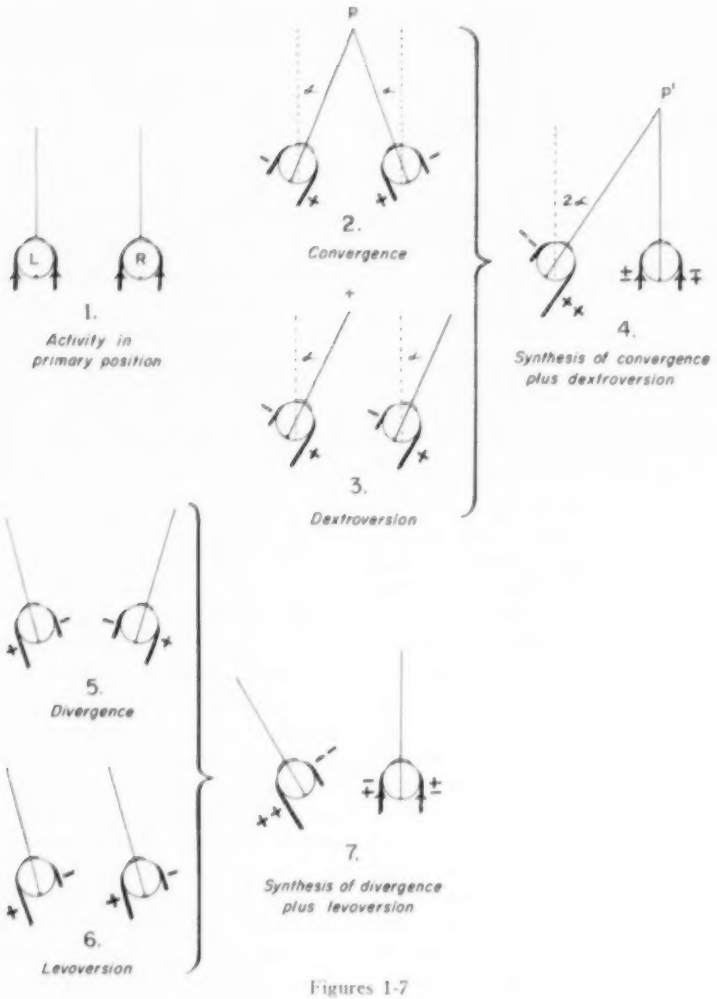
* References 2 and 3.



Figures 1-7

that if the medial rectus experienced an increased innervation it could be balanced by an equal increase of the lateral rectus, does not occur. This appears to have been the concept held by Hering, but in his day the reciprocal nature of inhibition and excitation was unknown. In the case of the eye on the side of the fixation object, for each unit of increased excitation of the medial rectus induced by convergence there is apposed an equal inhibition induced by the version. For each unit of inhibition of the lateral rectus induced by convergence there is apposed an equal excitation induced by the version. The resultant is the exact level of innervation for both muscles that existed before (Fig. 4).

In the case of the other eye the innervations of convergence and version are additive for both muscles; hence there occurs a greater medial rectus excitation and lateral rectus inhibition (Fig. 4). It is astonishing that the brain adjusts these innervations with such exquisite precision that no observable electromyographic alteration is noted in either muscle of the one eye, while the

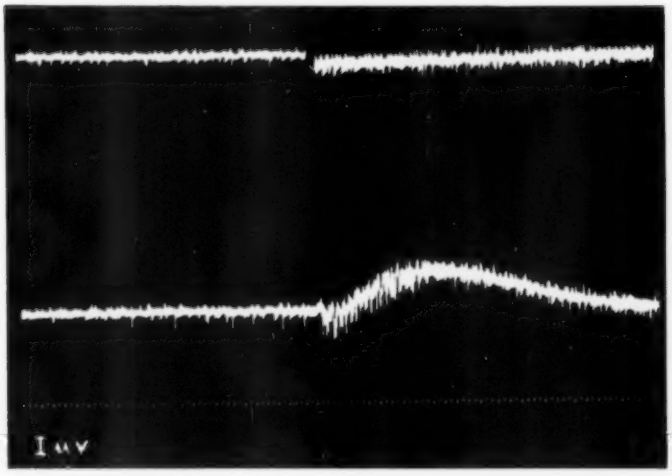


Fig. 8.—Left inferior oblique in a patient with paretic right superior rectus. Upper left, good eye fixing in primary position—primary deviation. Upper right, paretic eye fixing in primary position—secondary deviation. Lower, upshoot of inferior oblique.

onus of rotation is borne entirely by the other.

The application of the above findings to tropias is now evident. In the intermittent exotropes the fixating eye is in the primary position; the other eye deviates outward. The divergence impulse goes to the two lateral recti equally (Fig. 5) but is neutralized in the fixating eye by an opposite version (Fig. 6)—this is the essential and ineluctable requirement for maintenance of fixation. Consequently, there is no observable change in the innervations of its muscles, whereas those of the deviating eye suffer the double dose of divergence and version (Fig. 7). It is now apparent that ocular deviations are not simple, but are truly complex.

It would appear that the same line of reasoning applies to the eso deviations.

From these observations it is evident that the sensory apparatus polices the motor apparatus and that ophthalmologists must pay due heed to the sensorium, which is their sole ally in the control of oculomotor anomalies.

It is gratifying to realize that Hering's and Sherrington's Laws maintain their sway and find corroboration in the objective data of electromyography. It is a mark of the greatness of these men that the technologic advances of subsequent generations can only add new luster to their fame.

Additional evidence of this is seen in Figure 8 (from unpublished data of Breinin and Moldaver), which illustrates the truth of another of Hering's concepts—there is revealed the concrete proof of the increased innervation which characterizes secondary deviation. The recording from the left inferior oblique in a patient with a paretic right superior rectus shows the increased level of firing when the paretic eye fixes.

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Dacryocystography

II. The Pathologic Lacrimal Apparatus

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In a previous communication, we, with the use of a radiopaque dye (ethyl iodophenylundecylate; Pantopaque), demonstrated the anatomy and radiographic appearance of the normal lacrimal apparatus.[1] It was found that the time normally required for the contrast medium to disappear from the undiseased lacrimal passages was less than 30 minutes. After that length of time no dye—or only a trace—was found in the follow-up film. This finding was so consistent that it was possible to conclude that any system which retained a significant amount of the dye after 30 minutes, especially in the sac, was not functioning properly. It was emphasized that accurate evaluation of the dacryocystogram required correlation of the radiographic findings with the clinical history, as well as comparison of the lacrimal system on the involved side with that of the normal side.

In this presentation, we shall demonstrate some of the commoner pathologic conditions encountered in dacryocystography. The cases presented here were selected from a group of patients seen over a period of 10 years at the Washington University Clinics and affiliated institutions. Functional and anatomic blocking of the lacrimal passages will be discussed, and cases will be shown to illustrate the various syndromes.

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FUNCTIONAL BLOCK

A basic understanding of the behavior of ethyl iodophenylundecylate in the normal lacrimal system provides us with a valuable approach to the investigation of one significant group of patients who complain of tearing. These are the patients in whom irrigation and probing reveal no obstruction of the lacrimal passages. Heretofore, such a finding of patency of the system left little to be done therapeutically, since many practitioners felt that surgery was contraindicated. The physician was then left with the limited devices of repeated probings and irrigations and the use of local astringents and/or antibiotic eye drops.

As is well known, these methods more frequently than not meet with indifferent success, and the patients resign themselves to the perpetuation of the annoyance of a watering eye. In some cases, the persistent tearing may be complicated by intermittent bouts of recurrent dacryocystitis. This cycle of tearing, chronic irritation, and infection may be repeated several times, until a frank stenosis develops. It is at this time that the majority of surgeons feel justified in operating.

The radiographic demonstration of a persistent functional block in a chronically tearing eye is often an indication itself for dacryocystorhinostomy. These patients respond just as dramatically as do those with anatomic obstruction. The following case report illustrates a functional block in the lacrimal drainage system.

CASE 1 (E. Z.).—This 55-year-old white man gave a history of intermittent tearing of both eyes for the past seven years. In 1947 he had tearing of the left eye, which improved after repeated probings and irrigations of the lacrimal passages. For approximately two months prior to the time of the

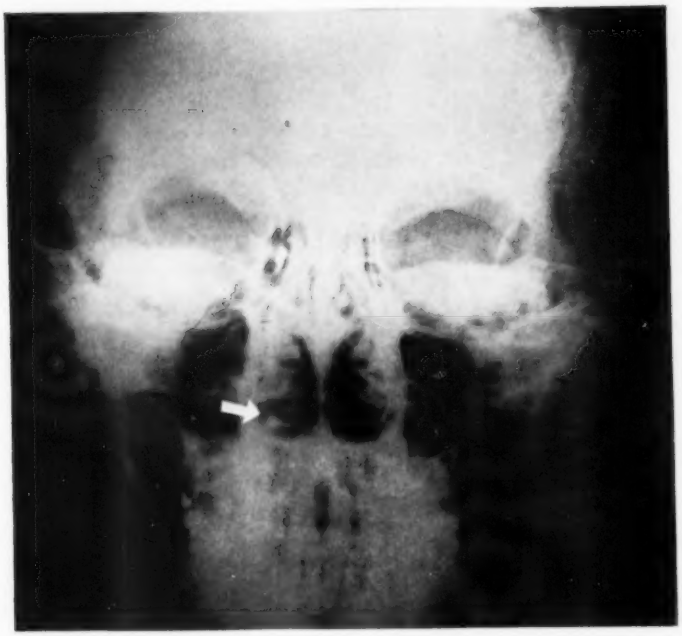


Fig. 1 (Case 1).—P. A. view. Arrow indicates dye under right inferior turbinate, demonstrating patency of the drainage system.

roentgen studies the patient had persistent tearing of the right eye. There had been no discharge, but there was some tenderness over the tear sac. The system was irrigated with ease, but there was no relief of his symptoms following irrigation.

Figure 1 demonstrates patency of the right passages, as evidenced by dye under the inferior turbinate (arrow). Figure 2, taken after 30 minutes, shows no change in the

Fig. 2 (Case 1).—P. A. view after 30 minutes. Arrow points to retained dye in sac, indicating a functional block.

moderately distended sac shadow (arrow), indicating retention of the dye and a functional obstruction of the system at the sac-duct junction. This patient was felt to be a candidate for right dacryocystorhinostomy.

EPIPHORA UNRELATED TO THE NASOLACRIMAL TRACT

Persistent tearing for reasons other than nasolacrimal obstruction may at times be responsible for unnecessary probings and surgery. The use of dacryocystography will support the ophthalmologist in the conservative approach to the therapy of such patients. The following case of neurogenic tearing demonstrates the assistance afforded by these roentgenographic studies.

CASE 2 (P. S.).—This 63-year-old white woman complained of severe tearing of the right eye which had its onset six years before, associated with a right hemicrania. The neurologic study was negative. There was no involvement of the left eye and no visual impairment in either eye. Prior to the onset of the present illness, and at intervals since then, there have been episodes of migraine characterized by hemianopsia and fortification phenomena, without accompanying headaches or exaggeration of the tearing.

The dacryocystogram shown in Figure 3 reveals patency and incomplete filling of the drainage system on both sides. The follow-up film showed no retention of dye after 30 minutes. Despite the persistence of tearing for six years, and despite the understandable urge toward surgical intervention, the radiographic proof of satisfactory drainage function negated any surgical approach and averted repeated probings.

PRESURGICAL VALUE OF DACRYOCYSTOGRAPHY

I. ANATOMIC BLOCK

As is true of other diagnostic adjuncts, increased familiarity with dacryocystography pays dividends in the form of additional information in each case. Therefore, it is now our practice to include this examination on every patient with persistent tearing. The films obtained aid us in selecting the proper surgical or medical therapy for each patient.

Fig. 3 (Case 2).—P. A. view. Arrows point to incomplete filling of both systems. Dye is present in the nasal floor, indicating patency on both sides.

Fig. 4 (Case 3).—P. A. view. Arrow shows location of block.

Fig. 5 (Case 4).—P. A. view. Arrow shows dye in upper duct.

Roentgenograms determine whether the obstruction is complete or partial, and the location of the block can be reported accurately. Three-fourths of the complete obstructions are found radiographically at the sac-duct junction (17 of 23 consecutive obstructions). In the remaining cases some of the residual dye is found in the duct. In the typical obstruction the dilated sac is round or oval. The dome of the pathologic sac fills above the confluence of the canaliculi, and the canaliculi may or may not be visualized.

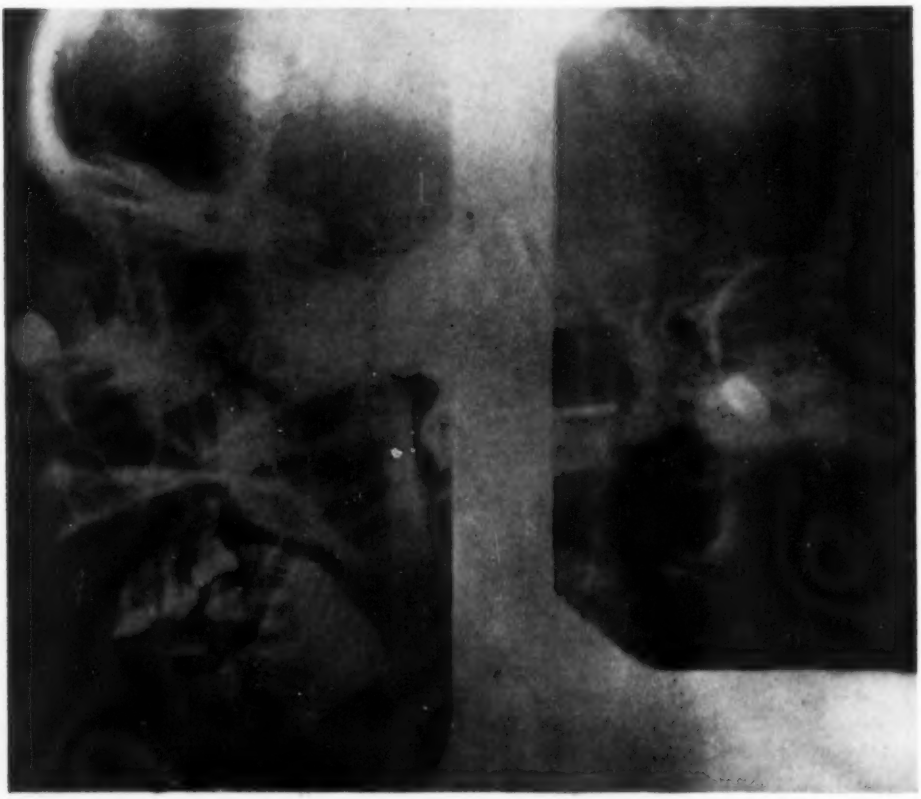
Case 3 (L. H.).—A 45-year-old white woman presented the complaint of intermittent bouts of pain and swelling over the right tear sac area for the past five years. The left side was not involved, and she had no other pertinent ocular history. Two days prior to hospital admission, the patient developed an acute inflammatory exacerbation in the right sac. The eye quieted with use of local heat and antibiotics. The dacryocystogram (Fig. 4) revealed a distended sac (shown by arrow), with a block at the sac-duct junction.

An obstruction in the midportion of the nasolacrimal duct is illustrated by Case 4.

Case 4 (S. O.).—This 65-year-old white woman presented the complaint of watering of both eyes of two years' duration. There was no history of any acute inflammatory episodes. Examination revealed conjunctival hyperemia and tearing of the left eye, but the right eye was entirely normal. The left nasolacrimal passages could be neither probed nor irrigated successfully, and mucopus was recovered in the conjunctival sac. The right side could be irrigated freely into the nose.

Figure 5 shows a posteroanterior view of the left side, with an irregular accumulation of dye filling the lower sac and the upper half of the nasolacrimal duct. The 30-minute film (not shown) was essentially the same.

Fig. 6 (Case 5).—Left, right sac, lateral view. Right, left sac, oblique view.



II. Atony of the Sac

The preoperative film also demonstrates the character of the lacrimal sac. It may be markedly stretched and atonic, or shrunken and stenosed. The large, atonic sac usually responds well to dacryocystorhinostomy. Extremely dilated sacs are well illustrated in the following case.

Case 5 (D. W.).—A 47-year-old Negro woman presented herself at the Washington University Eye Clinic with a history of poor vision of three years' duration and very large tumor masses in the region of the lacrimal sacs. Epiphora was not a presenting complaint. External examination revealed huge cystic lacrimal sacs filled with pus. Dacryocystograms confirmed this diagnosis and showed complete stenosis at the sac-duct junction.

Figure 6 shows a lateral view of the enlarged right sac and an oblique view of the dilated left sac.

The shrunken sac presents an obstacle to the surgeon employing the classical forms of dacryocystorhinostomy. In such cases, it is wiser to employ one of the techniques utilizing intubation of the system or, if this is not feasible, to excise the sac.

It should be emphasized that careful interpretation of the dacryocystogram is required to detect the occasional cases in which dacryocystitis has tended to obliterate the lumen of the sac. Partial visualization of the system is not in itself an indication of reduction in the lumen. The reduced shadow may result from incomplete filling with the dye or from hypertrophic and polypoid mucosal changes in the sac.

Moreover, a large mucocele is sometimes characterized by a block at the canaliculus-sac junction. Flow of the dye into the sac is impeded and may result in an inadequate sac shadow. It is our practice to attempt evacuation of the distended sac by manual expression before instilling the 1 cc. of dye; the amount of dye lost through back-flow into the conjunctival sac is then recorded. Later, when the films are reviewed, it is of value to know how much of the dye was lost in this retrograde fashion during the injection.

Case 6 (I. W.).—This 74-year-old white woman was first seen in April, 1953, with the history of having had a "pus bag" removed from the nasal angle of the right eyelids about 10 years earlier. Since that time she had had tearing of the right eye. About two years prior to the present examination she also began to have moderate tearing of the left eye, as well as some mucoid secretion in the right conjunctival sac. The symptoms have been unchanged since that time.

The posteroanterior view (Fig. 7) shows a slightly widened, blunted sac shadow on the right, with excellent filling of the canaliculi and no dye extending into the duct. (The 30-minute film, not shown, differed only in that the canaliculi had emptied.) The filling of the portion of the sac above the canaliculi and the visualization of the canaliculi, together with the notation that 80% of the dye had spilled back into the conjunctival sac during injection, strongly suggested that the lumen of the sac is reduced. This would be consistent with the history of a previous operation in which extirpation (or cauterization) was incomplete.

III. Fistula and Diverticula

One of the most dramatic uses of the dacryocystogram is found in the demonstration of fistulae and diverticula of the lacrimal sac. These findings occur most commonly after spontaneous rupture or incision for empyema of the sac. The late results of fistula formation are well recognized. It has been stated [2] that fistulae persist as long as there is obstruction to the normal outflow of tears, but these secondary openings will close once the normal tear drainage is reestablished. Using dacryocystography, one is able to determine the location, course, and extent of the fistula or diverticulum, as well as the state of the entire lacrimal tract. One of us (B. M.) has reported elsewhere [3] a patient in whom the roentgenograms confirmed the presence of normal lacrimal drainage, as well as a large persisting fistula, both of which had been functioning for 12 years.

Case 7 (R. K.).—This 18-year-old white youth reported having an operation on his "right eye" at the age of 6 years. Since that time he has had a

Fig. 7 (Case 6).—P. A. view, showing right canaliculi (arrows) and moderately distended sac, with obstruction at the sac-duct junction.

lacrimal discharge from an opening in the skin at the inferior orbital margin. Examination revealed a fistulous opening in the right lower eyelid. There was no swelling in the region of the lacrimal sac, but pressure over the sac produced a gush of tears from the skin opening. There was no laking of tears in the conjunctival sac. The left lacrimal apparatus was normal.

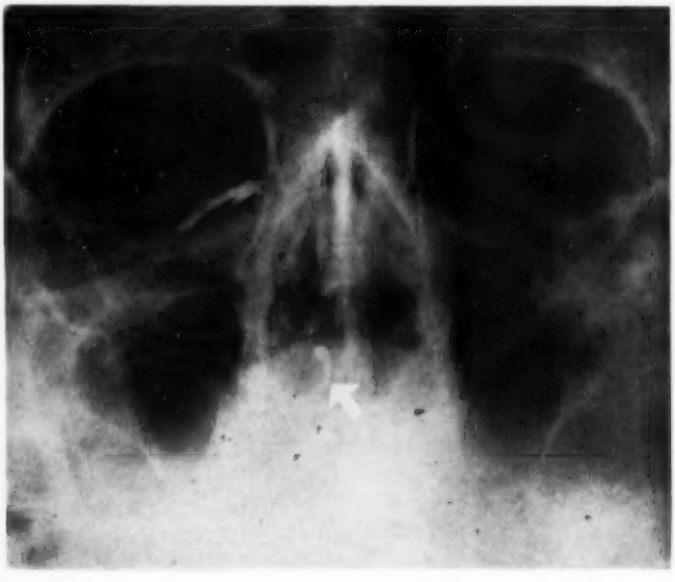


Fig. 8 (Case 7).—P. A. view of lacrimal fistula. Arrow shows dye in nose, indicating patency of the system.

Figure 8, a posteroanterior preoperative film, shows the extent of the fistulous tract. Patency is demonstrated by the accumulation of dye in the nose (arrow).

Demonstration of a diverticulum of the sac often provides the answer in the case of a persistent mucopurulent discharge from an otherwise clear sac.

CASE 8 (L. M.).—This 21-year-old white woman was first seen with an acute, tender swelling in the left lower eyelid, between the punctum and the nasal canthus. The lacrimal passages were readily irrigated, with no evidence of obstruction. Rhinologic examination and orbital-sinus roentgenograms were normal. Pain and tenderness persisted, and after one month the patient began to have a slight amount of mucoid discharge from the lower punctum. There was no history of tearing. Antibiotic therapy failed to eliminate the symptoms, and dacryocystograms were taken.

The dacryocystogram (Fig. 9) revealed a distended sac, to which was appended a broad diverticulum (shown by arrow) extending temporally along the inferior orbital margin. A small amount of the dye was found in the lower duct, indicating patency of the system.

POSTSURGICAL USES OF DACRYOCYSTOGRAPHY

I. DACRYOCYSTORHINOSTOMY

It is generally accepted that at least 75% of all dacryocystorhinostomies, irrespective of the technique employed, will be successful in restoring the lacrimal function. Many reports indicate a much higher proportion of successes. In those cases which prove to be unsuccessful, roentgenograms help to determine both the cause of failure and the necessary corrective approach. When postoperative radiographic studies are used, one should watch for some of the following possible causes of the persistent discharge:

1. Lacrimal sac diverticula not noted prior to surgery
2. Postoperative fistulization
3. Secondary closure of the dacryocystorhinostomy opening

Closure of the surgical opening may be caused by a bone fragment which was not removed during the surgery, by granulation tissue, by an organizing hemorrhage, or by

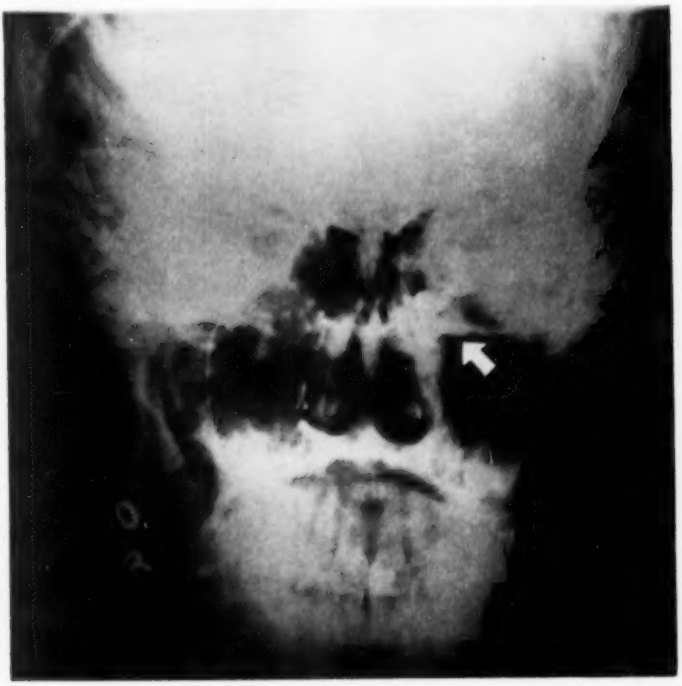


Fig. 9 (Case 8.—P. A. view, showing distended lower sac, with a broad diverticulum attached to the lower temporal aspect of the sac (arrow).

Fig. 10 (Case 9). — P. A. view, showing dilated sac, with complete block (arrow).

a flap of mucous membrane. In one case postoperative residual epiphora was found to be due to closure of the lower canaliculus at its junction with the sac. Apparently, this was caused by excessive traction on the canaliculus when the sac was pulled over to be anastomosed with the nasal mucosa. In this patient the radiographic findings were most important, since they provided the only means of confirming the patency of the sur-

Fig. 11 (Case 9). — Oblique view of same patient, showing distended sac (arrow).

gical anastomosis (by injecting the dye through the upper canaliculus). It was then possible to thread a polyethylene tube through the blocked lower canaliculus and into the nose by way of the intact surgical anastomosis. Leaving this tube in place for six weeks provided restoration of lacrimal drainage continuity and a final successful postoperative result.

II. Dacryocystectomy

From time to time, an embarrassing problem is encountered, when, following removal of the lacrimal sac, the patient continues to have mucus or mucopus discharging from the puncta. The cause may be an incomplete excision, particularly when the so-called "removal" consisted of incision and cautery of the sac. If the sac has been incompletely removed, it is usually the cupola which remains, since that portion is the most difficult to extirpate or cauterize. Another source of a persistent postoperative discharge in cases such as this may be found in an infected, dilated canaliculus. Identification of these residual pockets, radiographically, greatly facilitates their removal.

OTHER FACTORS

Among the radiographic findings which influence the management of chronic obstructive dacryocystitis are the following:

1. The condition of the paranasal sinuses
2. The position of the nasal septum
3. The amount of hypertrophy of the nasal turbinates
4. The presence of any osteomyelitis in the surrounding bony structures
5. The condition of the orbital and nasal bones following trauma, where fracture might be present
6. The presence of tumors of bone or soft tissue in the vicinity of the nasal lacrimal passages.

Several of these findings are illustrated in the following case histories.

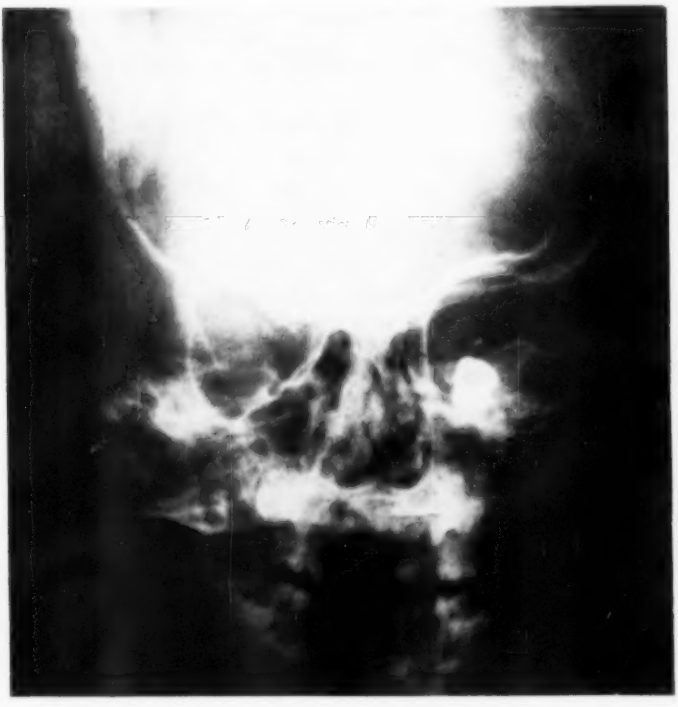


Fig 12 (Case 10).—P. A. view, showing markedly enlarged sac, apparent lateral displacement being due in part to multiple fractures and callus formation in region of the lacrimal fossa.

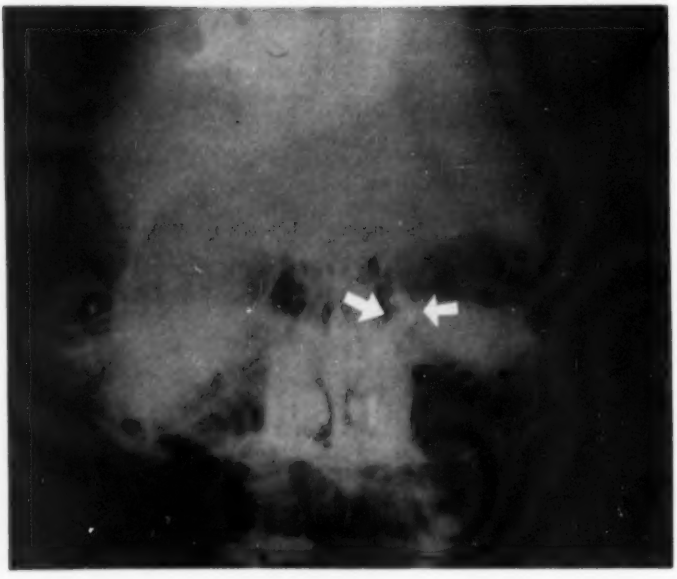


Fig. 13 (Case 11).—P. A. view, showing a kidney-shaped dilated lacrimal sac shadow, with concavity directed nasally (arrow).

Case 9 (N. J.).—This 25-year-old white woman had a left antral window operation performed for relief of chronic maxillary sinusitis. Tearing of the left eye was noted following the surgery, and after two weeks a subacute dacryocystitis developed. No local treatment was employed, and the patient was first seen in the Washington University Eye Clinic four weeks later. At this time, the left lacrimal sac was filled with pus and was moderately tender.

The dacryocystogram (Fig. 10) revealed a moderately dilated lacrimal sac, with complete obstruction (arrow). In the oblique view (Fig. 11), the antral surgery is partially indicated by an area of rarefaction contiguous with the lacrimal shadow. It was concluded that there had been surgical interference with the integrity of the nasolacrimal duct.

Case 10 (S. C.).—In June, 1951, when she was 2 years of age, the patient, a white girl, had been injured in an automobile accident. She suffered multiple fractures of the left facial bones and avulsion of the scalp and both eyelids. The avulsed skin flaps were sutured, and no further treatment was instituted at that time. An acute left dacryocystitis occurred one month after the accident, and since that time there have been recurrences of the dacryocystitis, treated in each instance with local antibiotics and heat. The patient was first seen at the Washington University Eye Clinic in October, 1953, for treatment of the tear-sac infection. Examination revealed lateral displacement of the left nasal canthus and an irregular bony callus formation occupying the position of the lacrimal fossa and extending over the inferior orbital margin, nasally. Much pus was expressed by pressure over the markedly distended sac.

The dacryocystogram revealed a markedly dilated lacrimal sac, with complete obstruction. There was irregularity and thickening of the inferior orbital margin and maxilla on the left, indicative of old fractures in this area.

Case 11 (S. L.).—This 43-year-old white woman first noted a swelling and tenderness over the right tear sac in May, 1953. The lacrimal passages on the right side were probed, and the symptoms disappeared in one day. In November, 1953, the patient was first seen by one of us (B. M.) with a recurrence of the same symptoms. Irrigation of the right sac and duct revealed patency, as well as a small amount of mucopus. A moderate soft swelling over the sac area was not reduced by irrigation or pressure.

The dacryocystogram revealed a distended right lacrimal sac (the photograph is reversed) with a kidney-shaped outline. The concavity in the shadow (indicated by arrow) corresponded to the position of the soft mass.

Because of this finding, as well as the irreducible nature of the mass, a tumor involving the lacrimal sac was suspected. At operation, an encapsulated tumor of the lacrimal sac was found, partially obliterating the lumen of the sac. The pathologic diagnosis was "neurofibroma of the lacrimal sac."

It is evident that the dacryocystogram, when combined with a preliminary scout film of the orbits and facial bones, provides a modus operandi for individualizing the treatment of such lacrimal disease as may be associated with trauma, tumor of the sac or in the area, or paranasal sinus disease.

INFANTS AND CHILDREN

When the usual methods of probing and irrigation have failed to produce a cure for epiphora in the child, the dacryocystogram, taken with the patient under general anesthesia, may help to locate the position of the block. The additional difficulties encountered in obtaining the assistance of the anesthetist may well be compensated by the corroborative evidence of the dacryocystogram, preparing the way for definitive surgery.

SUMMARY AND CONCLUSIONS

Routine use of radiography of the lacrimal passages is recommended in all cases of epiphora.

It was shown previously that, although the the nasolacrimal system may be patent by ordinary irrigation, impaired drainage function can be demonstrated by the dacryocystogram. This type of "functional block" may be an indication for dacryocystorhinostomy.

When patency of the lacrimal passages cannot be demonstrated by routine irrigation, the preoperative use of dacryocystography is indicated to show (*a*) the character of the structures adjacent to the sac, (*b*) the position and extent of the stenosis, and (*c*) the size and tonus of the sac.

Illustrative cases are presented to show some of the interesting types of pathology which may be demonstrated radiographically.

Following operative procedures, the dacryocystogram is useful in evaluating the results of the surgery.

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Permanent Bilateral Blindness Following the Use of Hexamethonium Chloride

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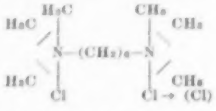
Hexamethonium chloride is a quaternary ammonium halide. Its formula is:



Sometimes the bromide is employed and in England the iodide is preferred, but the chloride is the most commonly used salt.

In the United States hexamethonium is sold as Methium (Warner-Chilcott Laboratories), Hexameton (Burroughs Wellcome & Company), Esomid (Ciba Pharmaceutical Products, Inc.), Bistrium (E. R. Squibb & Sons), and others. It is also combined with such antihypertensive drugs as hydralazine (Apresoline) and rauwolfine.

The tetra-, penta-, and hexamethonium compounds act by blocking both the sympathetic and the parasympathetic ganglia. The block, which is carried out by competition, occurs at the synapse. Vasoconstriction and autonomic tone are thereby reduced or abolished. In addition to use of hexamethonium in hypertension, the drug is being widely used in surgery, particularly in extensive operations, to diminish bleeding. As might be expected in a drug that may cause a fall of blood pressure from 260/160 to 90/50 in seven minutes, or a fall in systolic pressure of 100 mm. of mercury in a change from the supine to the sitting position, many systemic complications have been described, such as myocardial infarction, uremia, hemiparesis, thrombosis of cerebral vessels, tachycardia, postural hypotension, tinnitus, vertigo, dryness of the mouth, Raynaud's phenomenon, interstitial pneumonia, psychosis, and sudden death. Constipation and difficulty in micturition are complications especially to be avoided, because the drug is excreted through the intestine and kidneys. Retention may thereby produce hexamethonium poisoning.

The systemic effects of the drug are discussed in the papers of Galen,[1] Rønnov-Jessen,[2] Hilker,[3] Beaconsfield,[4] Smith,[5] Schroeder,[6] Moyer,[7] and Moser.[8]

The effect on the eyes of hexamethonium, of course, includes mydriasis and cycloplegia. In addition, references are found to fall in intraocular tension, clearing of exudate and hemorrhage in the retina,* hemianopsia, temporary unilateral blindness, epiphora, periorbital edema, and acute glaucoma.

It is extremely difficult to evaluate what the immediate cause of some of the ocular symptoms may have been. Because the authors knew that cycloplegia resulted from the use of hexamethonium, they ascribed—often apparently without so much as inspecting the fundus—such symptoms as "blackouts," "protracted dimness of vision," "blurring of vision," and others to paralysis of accommodation. In order to reach a conclusion, the ophthalmologist requires more information than is available in the purely

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* It has been used mixed in the same syringe with insulin in the treatment of hypertensive diabetics with "diabetic nephropathy."[9]

medical reports. Fortunately, however, ophthalmologists have made observations from time to time. For example, Goldsmith and Hewer [10] reported a case of unilateral amaurosis with partial recovery in a patient given hexamethonium to control bleeding during a radical mastectomy. The behavior of that case (apart from its more favorable outcome) closely parallels the report presented below.

Since mydriasis is an accompaniment of treatment with hexamethonium, the effect on intraocular pressure has concerned some of the workers. Hilker,[3] for instance, says that its use is contraindicated in glaucoma. Cameron and Burn,[11] however, actually used the drug in the presence of known glaucoma, producing a slight fall in intraocular pressure. They cite a case in which acute glaucoma occurred during use of the drug but nothing was known of the previous status of the eye, and they are inclined to look upon the occurrence as coincidental. Indeed, Rycroft and Romanes [12] have found the tension to fall so low that it could not be measured, and the cornea was concave. The consensus seems to follow the opinion of Couadau and Campan,[13] who found the fall in intraocular pressure true but variable. Barnett [14] and others have pointed out that retinal hemorrhage and exudate lessen or disappear after reduction of the blood pressure by hexamethonium. However, McMichael [15] has stated that the absorption may be delayed, and that there may be even a temporary increase in exudate.

The reader who wishes to study further the pharmacology of the quaternary ammonium compounds is referred to the works of Goodman and Gilman,[16] Paton and Zaimis,[17] and Shackman and associates.[18]

REPORT OF A CASE

A 34-year-old Negro woman was admitted to the Presbyterian Hospital, complaining of shortness of breath on exertion, blurred vision, and a vague pain in the left flank, all of two weeks' duration. She had known of "high blood pressure" for about a year. Her vision had been recorded elsewhere a week before as 20/70 in the right eye and 20/30 in the left, unimproved, but no hemorrhages or exudates were seen at that time. Convergence was noted as "poor." Previous and family histories were noncontributory.

Examination revealed that her temperature was 97.6 F, the pulse rate 86, and her respirations 18, per minute. She weighed 114 lb. Her blood pressure was 260/160, left arm, and 270/170, right arm. Urinalysis showed specific gravity of 1.012, 4+ albumin, and 60-90 red blood cells, 30-34 white blood cells, and no to one cast (granular), per cubic millimeter. There was a trace of glucose, but serum sugar was 95 mg. per 100 cc. Urea nitrogen was 26 mg. per 100 cc.; intravenous pyelography was negative, and the phenolsulfonphthalein test was 20%. An x-ray of the skull was negative, but x-ray of the chest showed moderate cardiac enlargement, hypertensive in outline. There was no evidence of pulmonary congestion. The Kolmer test was negative, the Mazzini test 1+, and the phentolamine (Regitin) test negative. The electrocardiogram was within normal limits, and the sedimentation rate 55 mm. in one hour. The blood count showed hemoglobin 11 gm. per 100 cc.; 2,370,000 red cells, and 6450 white cells.

She was given 6 mg. of hexamethonium chloride intramuscularly. The blood pressure was recorded as 240/136 and taken at one-minute intervals thereafter. The second reading was 236/140, the third 222/130, the fourth 190/110, and the fifth 180/110. At this point the patient complained that her vision was blurred. Since the cycloplegic action of hexamethonium was known to the physician in charge, no concern was felt at this time, and no ocular examination was made.

In a few minutes, however, the patient stated that she was blind. Examination now revealed that vision was reduced to perception of light in the right eye and to no perception of light in the left eye. The pupils were widely dilated, the right reacting slightly to light only, the left not at all. There was slight pain on rotating the eyes and on pressure over the globes, but none along the course of the temporal arteries. The media were clear, the discs of good color, and the arteries greatly narrowed, in places being reduced to fibrous cords. The retina surrounding the discs was a little edematous. An occasional cotton-wool patch and a few hemorrhages were seen, predominantly superficial. Classification was Grade III+, A. O. S.

The hexamethonium was discontinued for a while but was resumed when it became apparent that the vision was not returning and the patient's blood pressure was rising.

In a week temporal pallor of the discs appeared and the exudates increased, so that well-defined fan figures appeared at the maculas. The patient subsequently underwent sympathectomy, but the discs are now quite atrophic and the posterior poles disorganized by extensive hemorrhage and exudate.

COMMENT

The retinal signs and symptoms in this case are almost identical to those sometimes produced by systemic collapse or exsanguination or both. Among the mechanisms suggested as the immediate cause is hemoclastic shock, anaphylactic crisis, or toxemia due to hemolysis.[19] Nevertheless, the precise method by which the effect is produced remains unknown.

SUMMARY

Hexamethonium is a quaternary ammonium compound in wide use to lower high blood pressure and to reduce bleeding in extensive surgical operations. Four minutes after a patient with essential hypertension was given hexamethonium chloride intramuscularly her vision began to fail, and in a few minutes thereafter she became totally and permanently blind.

This presentation is a factual one, without attempt at analysis or evaluation. The reported case proves very little one way or the other. It does, however, suggest that ophthalmologists may well hold the quaternary ammonium compounds in a somewhat skeptical regard until more is known about their ocular effects.

Dr. Robert F. Loeb and his staff at the Presbyterian Hospital permitted the report of this case.

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Case Reports

OPTIC NERVE SHEATH AND SUBHYALOID HEMORRHAGE AS A COMPLICATION OF ANGIOCARDIOGRAPHY

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and
FRANK B. WALSH, M.D., Baltimore

OUR PREVIOUS studies[1] on optic nerve sheath hemorrhage included one case which seemed unique as regards the possible complications of angiography. This communication summarizes the important features of that case.

In brief, this patient developed massive unilateral optic nerve sheath and intraocular subhyaloid hemorrhage on the side on which the carotid artery was injected with 70% iodopyracet (Diodrast). There was only a small amount of blood in the left subdural optic nerve space. No intracranial meningeal hemorrhage was found at autopsy.

It has been stated by other authors[2] that in cerebral subarachnoid hemorrhage blood is forced under pressure through the optic foramen. Since no intracranial meningeal bleeding occurred in this case, it is evident that the nerve sheath hemorrhage can occur as an isolated phenomenon.

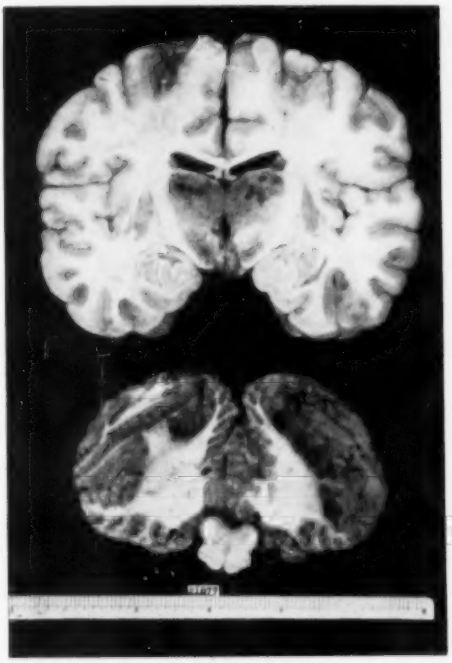

Fig. 1.—Gross specimen of brain showing scattered petechial hemorrhages in the cerebral cortex, thalamus, pons, and cerebellum.

REPORT OF A CASE

R. R., a 36-year-old white woman, had had congenital heart disease with cyanosis since birth. Studies revealed polycythemia and congenital heart deformities consisting of interventricular septal defect, patent ductus arteriosus, truncus arteriosus, and transposition of the great vessels. Intra-arterial angiocardiography was attempted, a catheter being passed by way of the left brachial artery to the region of the aortic arch. Twenty-two cubic centimeters of 70% iodopyracet was then injected rapidly. This was immediately followed by generalized convulsions and coma. X-rays revealed that the catheter was facing the right carotid artery and the dye had all entered this vessel. Death followed in three hours.

Autopsy revealed a normal cranial cavity with no meningeal hemorrhage either over the convexity or at the base of the brain. There was a well-defined cerebellar pressure conus. Scattered petechial hemorrhages were noted in the occipital cortex, thalamus, cerebellum, and pons, appearing like acute hemorrhagic encephalopathy (Fig. 1). The pathological microscopic findings were capillary hemorrhages in those areas in which gross lesions were visible and perivascular polymorphonuclear cell infiltration. The relative preservation of nerve cells and glia in these areas indicated that these lesions were not hemorrhagic infarcts (Fig. 2). Posterior segments of the eyes showed profuse optic nerve

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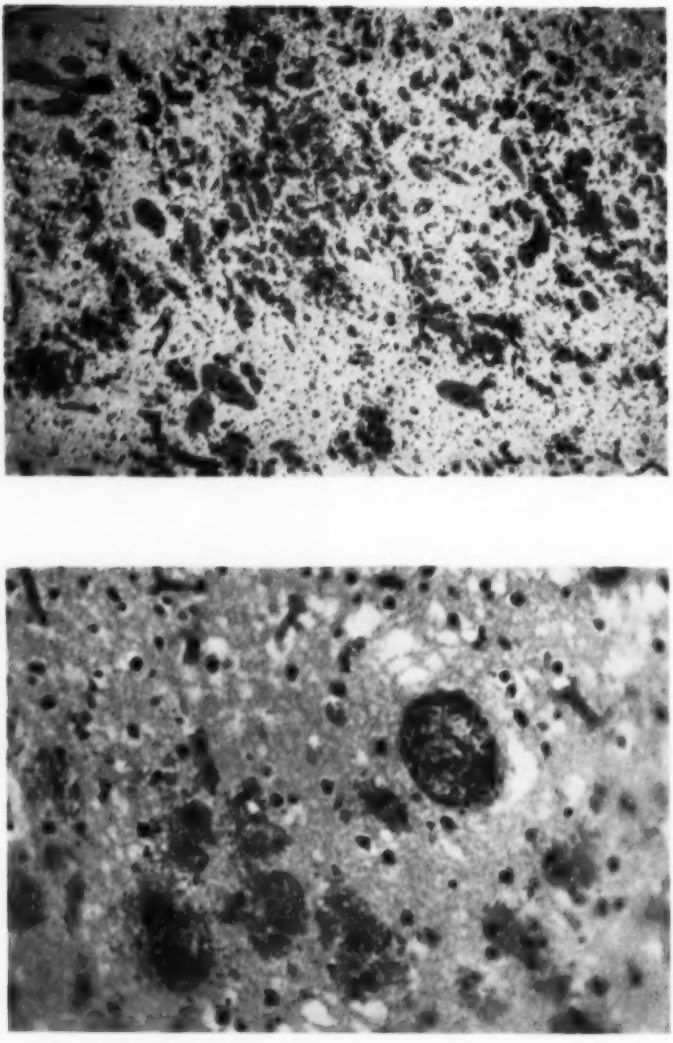

Fig. 2.—Above, microscopic section of occipital cortex, showing capillary hemorrhages. Reduced to ⅜ of mag. × 66. Below, high-power view of occipital cortex, showing capillary hemorrhages, perivascular polymorphonuclear cell infiltration, and preservation of nerve cells and glia in these areas. Reduced to ⅜ of mag. × 350.

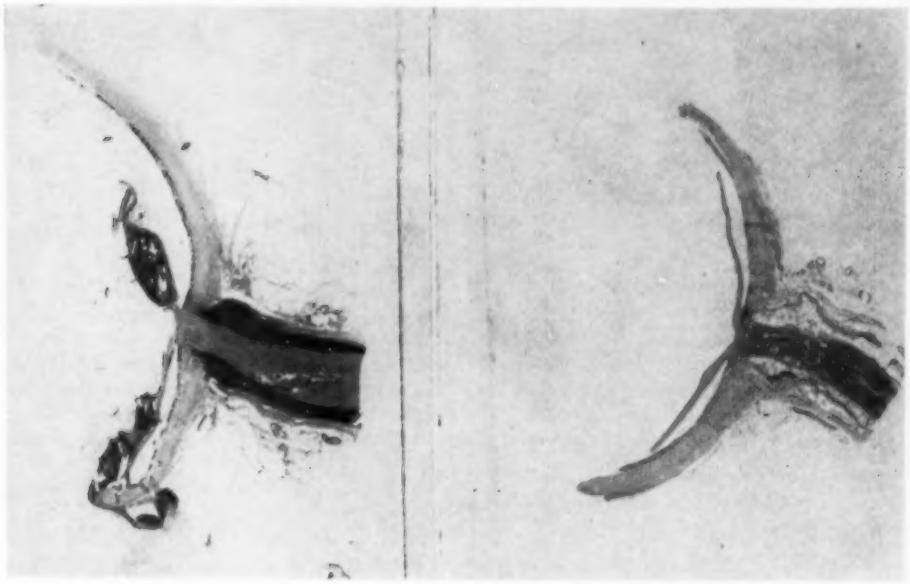

Fig. 3.—Posterior segments of the eyes, showing profuse optic nerve sheath hemorrhage in the subdural and subarachnoid spaces, plus subhyaloid and vitreous hemorrhage on the right. On the left there is only minimal fresh blood in the subdural space.

sheath hemorrhage invading the subdural and subarachnoid spaces, plus massive subhyaloid and vitreous hemorrhage on the right. On the left there was only minimal fresh blood in the subdural space (Fig. 3).

CONCLUSION

This case demonstrates an unusual complication of angiocardiography. In addition, the pathological findings show dramatically that isolated optic nerve sheath and intraocular hemorrhage may occur in the absence of intracranial meningeal bleeding. Such isolated venous hemorrhages occur as a result of intracranial venous stasis when there is a rapid rise in intracranial pressure.

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BASOSQUAMOUS-CELL CARCINOMA OF THE ORBIT

DONALD W. DEERING, M.D., Houston, Texas

THE FOLLOWING case is presented for two reasons: (1) to emphasize the importance of differentiating between a basal-cell and a basosquamous-cell carcinoma and (2) to demonstrate the value of employing the modified Krönlein procedure [1] in exploring the orbit in unexplained exophthalmos.

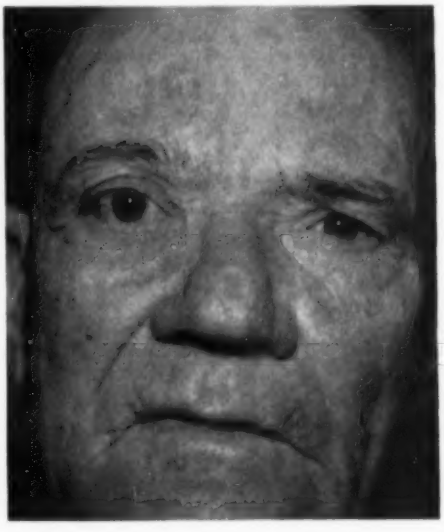
Approximately 10% of skin carcinomas about the face are mixtures of the basal- and squamous-cell types.[2] Some pathologists use the term basosquamous-cell carcinoma to indicate the presence of both cell types.[3] Such basosquamous-cell carcinomas do not follow the local invasive course of basal-cell carcinomas but, instead, show a tendency to infiltrate deeply and metastasize in the manner of squamous-cell carcinomas.[2] Therefore the importance of differentiating a basal-cell and a basosquamous-cell carcinoma cannot be overemphasized.

REPORT OF CASE

E. T., a 56-year-old white rancher, entered the Veterans Administration Hospital, Houston, Texas, in August, 1954, with a history of left frontal and supraobital pain since March 1, 1954. For about two months prior to the onset of the pain the patient had been troubled by numbness and tingling about the left orbit. One week after the development of the left orbital pain he noticed that his left eye was more prominent than the right, and since then the exophthalmos has been progressively increasing.

Examination of the eyes revealed the vision to be correctible to 20/20 O.D. and 20/25 O.S. The intraocular tension bilaterally was 17.0 mm. Hg (Schiøtz). A marked proptosis of the left eye was present (Figs. 1 and 2). The Hertel exophthalmometer readings, with a base line of 110 mm., were 15 mm. O.D. and 24 mm. O.S. There was marked engorgement and dilatation of the bulbar conjunctival and episcleral vessels over the superior temporal quadrant of the left globe (Fig. 2). No pulsation was felt upon tactile compression of the left globe, and marked resistance was encountered upon attempting to force the globe inward. No bruit could be detected with a stethoscope. There was limitation of abduction of the left eye with an apparent paresis of the left lateral rectus muscle. Perimetric and tangent screen fields were normal. The anterior and posterior segments bilaterally were normal except for an early nuclear cataract, O.S. The remainder of the physical examination was essentially noncontributory except for the following findings: The patient had approximately 20 round, white scars on the skin of his face. Several of these scars were located on the left cheek and eyebrow (Fig. 1). These scars developed after previous suspicious skin lesions had been fulgurated, on June 19, 1954 (biopsies were done

Fig. 1.—Marked exophthalmos of the left eye.



Submitted for publication June 15, 1955.

Fig. 2.—Engorgement and dilatation of bulbar conjunctival and episcleral vessels.

Fig. 3.—The patient's left orbit two months postoperatively, following a radical exenteration and resection of the lateral bony wall of the orbit.

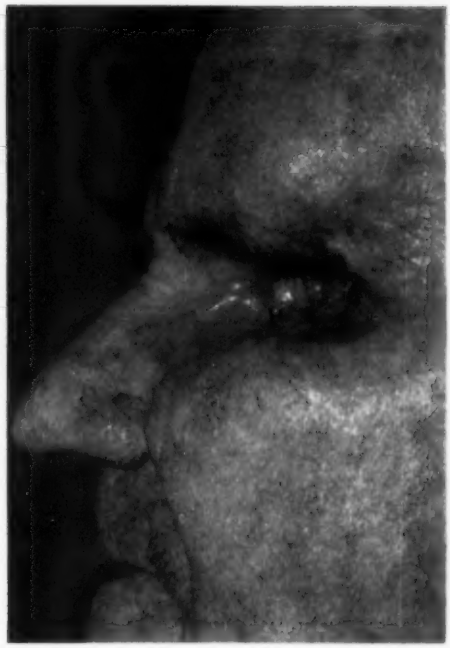
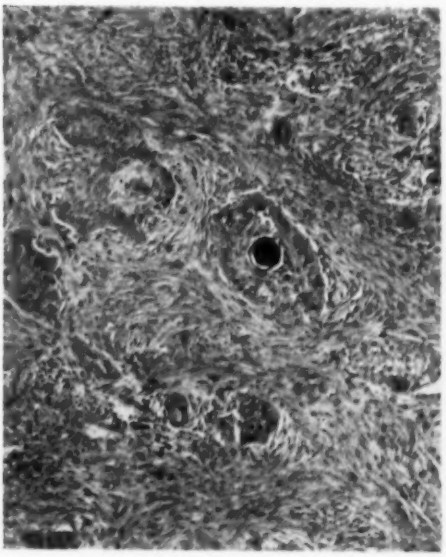


Fig. 4.—Lateral view of the patient's left orbit two months postoperatively, following a radical exenteration of the orbit and resection of the lateral wall of the orbit.

Fig. 5.—Typical area of squamous-cell carcinoma with epithelial nests and prickle cells. Reduced about ⅕ from mag. × 100.



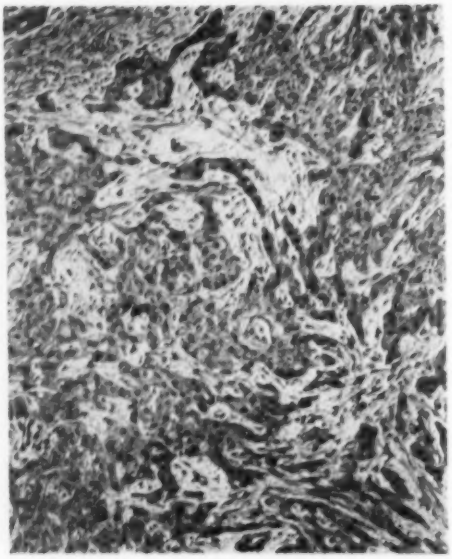


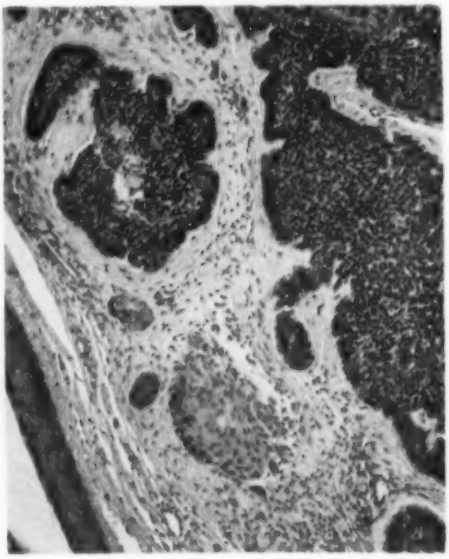
Fig. 6.—Another area of the orbital tumor. The cell pattern here is more on the order of a basal-cell tumor, with the presence of basophilic staining and development of the cells in cord-like patterns. Reduced about ⅓ from mag. × 100.

on three, and two were found to be basal-cell carcinoma).

Laboratory Studies.—Serology negative; urinalysis normal; hematology essentially normal. Blood chemistry: serum bilirubin 0.15 mg., cholesterol 181 mg., protein-bound iodine 4.7 mg., urea nitrogen 12 mg., and fasting blood glucose 100 mg., per 100 cc. Spinal fluid: pressure 123 mm.; cell count 1 per cubic millimeter; sugar 75 mg. per 100 cc.; total protein 29 mg. per 100 cc.; colloidal gold curve 0000000000; serology negative.

Hospital Course.—After the patient's admission to the hospital numerous diagnostic studies were undertaken. X-rays of the skull (specifically of the left orbit and optic foramen for evidence of tumefaction or bone destruction), sinuses, chest, long bones, and pelvis were all normal. No evidence of hyperthyroidism or of disturbed liver function was found. A left carotid arteriogram, done on Aug. 20, 1954, failed to reveal any vascular abnormality. On Aug. 24, the patient was seen by the ophthalmology staff, and a presumptive diagnosis of retrobulbar tumor, etiology unknown, was made. On Sept. 8 a diagnostic dose of 500μc of radioactive phosphorus was administered intravenously to the patient; however, subsequent Geiger counter studies were indeterminate. Therefore, on Sept. 10 a modified Krönlein lateral orbitotomy[1] was done on the left orbit. Upon elevating the orbital process of the zygomatic bone, a large, avascular tumor mass was encountered. The malignant tissues had invaded the lateral wall of the orbit and completely surrounded the optic nerve from globe to optic foramen. The globe itself was not invaded. A radical exenteration of the orbit was done, along with resection of the lateral bony wall (Figs. 3 and 4). The pathological report was basosquamous-cell carcinoma, primary site unknown (Figs. 5 and 6). Inasmuch as basosquamous-cell carcinoma of the orbit is not a primary tumor of the orbit but, instead, must represent a secondary site or a metastasis, our attention was directed toward determining the primary site. The cornea, conjunctiva, caruncle, lids, etc., were closely examined, but no evidence of a suspicious lesion could be found. A Caldwell-Luc operation done on the left maxillary sinus revealed the sinus to be entirely normal. We were then confronted with a diagnostic stalemate until we recalled the previously treated skin lesion about the left eye. Reexamina-

Fig. 7.—Basosquamous (mixed)-cell carcinoma. The deeply basophilic cells in cord-like patterns are characteristic of basal-cell carcinoma, but in the upper left-hand corner of the photomicrograph is the circumscribed mass of acidophilic-staining cells with the beginning development of an epithelial nest and, as can be seen on closer examination, many mitotic figures; this is characteristic of a squamous-cell carcinoma. Therefore this tumor is of the mixed-cell type and is a basosquamous-cell carcinoma. Reduced about ⅓ from mag. × 100.



tion of one of the two biopsy specimens that had been taken revealed the skin tumor to be a mixed basal-cell and squamous-cell carcinoma (Fig. 7) instead of a pure basal-cell type, as previously reported. This, we felt, was evidence enough to incriminate the fulgurated skin lesions about the left eye as the primary site for the basosquamous-cell carcinoma of the left orbit.

SUMMARY

This case is presented as one of a basosquamous-cell carcinoma of the orbit arising from previously fulgurated skin lesions about the eyebrow and cheek. It aptly demonstrates the necessity of obtaining histological study on all skin tumors and the importance of differentiating between a basal-cell and a basosquamous-cell carcinoma. The modified Krönlein procedure gave excellent exposure of the orbital tumor and simplified the subsequent exenteration of the orbit and resection of the lateral bony wall of the orbit.

Veterans Administration Hospital.

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Clinical Notes, New Instruments and Techniques

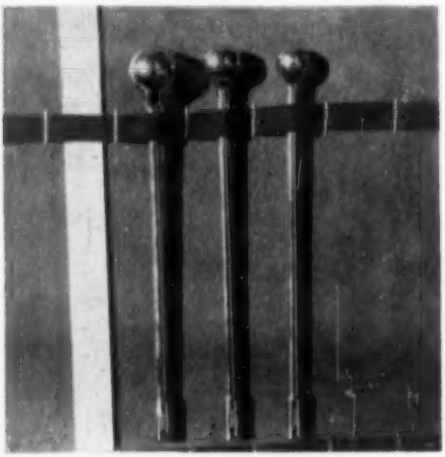
AN ORBITAL COMPRESSOR

ALBERT C. ESPOSITO, B.S., M.D., Huntington, W. Va.

THE USE of an orbital compressor in ocular surgery is not new, for a review of ancient writings reveals that a type of orbital compressor or conformer was used to stop hemorrhages after loss of the eyeball or after the eyeball had been removed surgically. The present use of a conformer is not universal, but, in view of its many advantages, it is felt that possibly it should be more frequent. The instrument is a definite means of applying gentle pressure for hemostasis and control of postenucleation bleeding. It can be placed in hot sterile saline solution, and thus warmed, then placed as a tampon inside the postenucleation cavity of Tenon's capsule to control bleeding. The sac and the muscles may be made ready for sutures and the implant made ready to be placed therein. It has been found that the conformer reduces the time and amount of postenucleation bleeding.

Submitted for publication May 11, 1955.

Fig. 1.—Orbital compressors in three sizes—12, 16, and 18 mm. head sizes with 14 mm. shaft—to fit most instrument cases and for ease in manipulation.



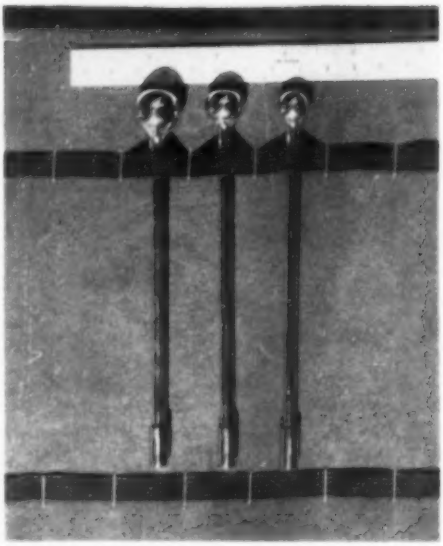


Fig. 2.—Orbital compressors to show head size, as compared with a millimeter rule.

In this respect, the search for a compressor which would be small enough that it could be easily placed in the usual carrying case, such as the Storz Instrument Company case, and that could be sterilized by either cold sterilization or autoclaving has been unsatisfactory. Accordingly, new-sized compressors were adopted and were made up by Storz Company, of St. Louis, for use. They have been found to be eminently satisfactory. The compressors have been made up in three sizes: a 12, 16, and 18 mm. ball at the end of

the 14 cm. shaft, and this has made the compressor of a size equal to almost all other ocular surgical instruments, and of a weight which is comparable to that of other ocular instruments. The head sizes make them readily adaptable to all-sized sockets; the length makes them adaptable for use in small pans for cold sterilization, and they are also easily stored in a carrying case.

We feel that the use of the compressor is a valuable adjunct in ocular surgery, and we believe that compressors as planned, and as made up by Storz Instrument Company (Figs. 1 and 2), are much easier to store in the instrument case, to autoclave, and to use than any previously available. Moreover, by more nearly conforming to the size of other ocular instruments, these compressors are readily adaptable to any set of ocular surgical instruments.

First Huntington National Bank Building.

Registry of Interesting Cases

It is the purpose of this section to record cases on the basis of interest only. No complete review of the literature is attempted and no claim for priority is implied except when specifically stated. Publication of case reports is subject to the concurrence of the Editorial Board on the interesting aspects of the case. It is requested that the reports submitted be as brief as is consistent with inclusion of the pertinent facts, bear a title that is as specific as possible, be prefaced by a paragraph that states why the author feels the case is of interest and be accompanied with photographs whenever possible.

AN UNUSUAL CASE OF FILAMENTARY KERATITIS

CHRONIC relapsing keratitis, characterized by coarse filaments occurring in eyes with a normal supply of tears, is an uncommon condition of unknown etiology. Berliner [1] states that corneal filamentary formation is nearly always associated with conjunctivitis. The case reported here is unusual in that the patient had a marked right convergent strabismus and a filamentary keratitis that was limited to the upper nasal quadrant of the right cornea. The filaments were never found elsewhere on the cornea. This area was precisely the portion of the cornea which was constantly covered by the tarsal conjunctiva of the upper lid. Moreover, this conjunctiva was frequently observed to be injected and showed a mild follicular hypertrophy. Since the right eye was more or less fixed in a position of extreme convergence, the upper nasal quadrant of the cornea was presumably in almost constant contact with this abnormal conjunctiva. Normal evaporation of tears on the epithelial surface of the cornea could not take place in this area. After the failure of various types of local treatment to control the severe recurrent attacks of pain, a strabismus operation was performed on the right eye two years ago. This operation was performed on the theory that the above-described condition might be responsible for the relapsing filamentary keratitis. Since we knew of no similarly treated case, it is considered of interest to report our experience with this patient.

REPORT OF A CASE

The patient, a 49-year-old white man, was first seen in the outpatient department of the Massachusetts Eye and Ear Infirmary on April 23, 1951. He stated that he had had intermittent pain, redness, photophobia, and lacrimation for the past two years. His right eye had been markedly convergent since early childhood, and the vision in this eye had always been poor. He had consulted numerous ophthalmologists during the course of the preceding two years, and many local medications had been prescribed, including silver nitrate, cortisone, etc. Some of these medications relieved the immediate attack, but he continued to have recurrences. Examination showed that the vision in the right eye was 5/300 and the vision in the left eye 20/20—1, with glasses. The right eye showed a convergent strabismus of over 50 degrees and was considerably hypertrophic. There was marked overaction of the right inferior oblique muscle. The right eye could not be abducted beyond the midline. Slit-lamp examination of the fluorescein-stained cornea showed an epithelial spiral at 1:00 o'clock, surrounded by a small area of epithelial erosion. The patient was subsequently examined on several occasions. On all occasions when he had complaints, filaments were found in the upper nasal quadrant of the right cornea. He was treated with 0.5% methylcellulose drops four times a day in the right eye and petrolatum ointment, to be used at night. The cornea was cauterized with 10% trichloroacetic acid. Four weeks later, several large epithelial spirals and one punctate staining area were observed in the upper nasal quadrant of the right cornea. The eye appeared to have a normal supply of tears, and

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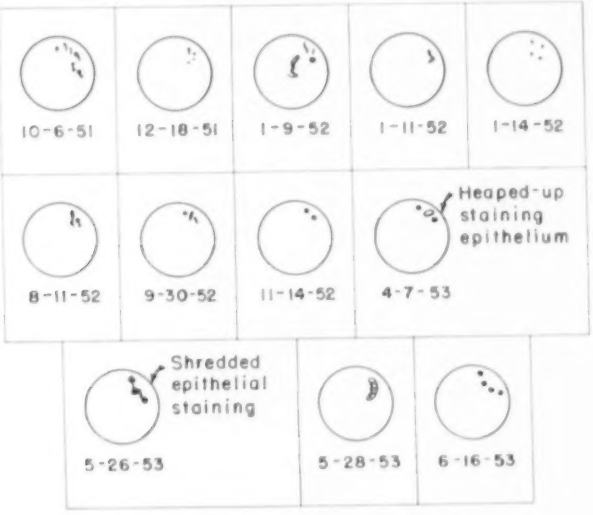
From the Massachusetts Eye and Ear Infirmary and the Harvard Medical School.

during an attack there was actually excessive tearing. A Schirmer test was negative. A conjunctival smear showed only an occasional polymorphonuclear leucocyte. There were no eosinophiles or inclusion bodies. Culture showed no growth after 10 days. On many subsequent occasions the local instillation of 1% silver nitrate, followed by irrigation with isotonic saline, was used. Most of these treatments gave a fairly dramatic relief of symptoms, but the attacks became more and more frequent over a period of one and one-half years.

Eventually, both medial rectus muscles were recessed 5 mm.; the right lateral rectus muscle was resected, and a myomectomy of the right inferior oblique muscle was performed. This resulted in straightening of the right eye and a more nearly normal relationship between the



Location of filaments and staining areas.

cornea and the lid. The patient has not had a single attack of filamentary keratitis since this operation. The accompanying Chart shows the location of the filaments and staining areas observed during each examination. It seems reasonable to conclude that the contact of the conjunctiva of the upper lid with the upper nasal quadrant of the cornea was responsible for the filamentary keratitis.

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115 Bay State Rd.
Boston

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OPTICOCILIARY NEURITIS

THE ASSOCIATION of optic neuritis with internal ophthalmoplegia, that is, paralytic mydriasis with paralysis of accommodation, has been termed opticociliary neuritis. Few cases have been reported in the literature. Deusch [1] and Best [2] each described one, and Rieger,[3] in 1952, reported two more cases of what he called acute ciliary ganglionitis. As far as can be determined, the following case is the fifth to be reported.

REPORT OF CASE

The patient, a 21-year-old white woman, had been in good health until December, 1952, when she suddenly developed blurred vision of the left eye. Since there was no improvement, she consulted an optometrist one month later and was told she had an "infection of the nerve" and was given reading glasses. Two months after the onset, vision returned to normal. Shortly thereafter, a friend pointed out to her that the pupil of the right eye was dilated. On covering the left eye, she found the vision of the right eye to be blurred. An ophthalmological examination at that time, by Dr. Paul W. Tisher, of New Britain, Conn., revealed the best vision in the right eye to be 20/400. The pupil was fixed and widely dilated, with complete absence of pupillary response to accommodation-convergence. The fundus was normal. Visual field examination showed the presence of a large sickle-shaped central scotoma. The patient was given a series of 20 vitamin B_{12} injections. There was slight improvement in pupillary reactions, but the pupil remained dilated and the central scotoma persisted.

Three weeks later, the patient had transient weakness of the right arm, lasting one day, followed by weakness of the right leg, again lasting one day. Neurological examination was negative except for absence of the Achilles reflex and questionable slight weakness of the right arm. X-rays of the skull and sinuses were negative. There was then gradual improvement in vision O. D., but the pupil remained dilated.

In June, 1953, vision in the right eye was 20/50, correctible to 20/20. Vision in the left eye was 20/25. The right eye was externally normal. The pupil was 8 mm. in diameter and reacted very slightly to light, directly and consensually. The media were clear, and the fundus was normal. The left eye was normal in all respects. The amplitude of accommodation O. D. was zero, as compared with 6.5 D., O. S. Visual fields were completely normal, both to white and to colored test objects. Two drops of 2.5% methacholine (Mecholyl) chloride were instilled in each eye. Within 30 minutes the pupil of the right eye had come down to 4 mm. in diameter. There was no effect on the left pupil.

One month later, vision O. D. had improved to 20/20 without correction. The pupil was 7.5 mm. in diameter, and reacted slightly to light, contracting to 6.5 mm., as compared with 3 mm. O. S. The amplitude of accommodation was now 2 D.

In August, eight months after the onset, vision O. D. was 20/15. The pupil was 8 mm. in diameter, contracting 2 mm. on exposure to bright light or in accommodation-convergence. The amplitude of accommodation was now 4.5 D. Visual fields were normal.

The patient was seen again in February, 1954, one year after the onset. At this time vision O. D. was 20/13 without correction. The pupil O. D. was 7 mm. in diameter, as compared with 4 mm. O. S., at ordinary room illumination. Pupillary response to light and in accommodation had improved, the pupil then contracting to 4 mm. The response was brisk. Twenty minutes after the instillation of 1 drop of 2.5% methacholine the pupil of the right eye contracted to 4 mm. in diameter, with no effect on the pupil of the left eye. The fundi remained normal, as were the visual fields. The amplitude of accommodation was now 6.5 D., O. U. The patient had no complaints other than her anisocoria.

Two findings here are worthy of note: one, the dissociation of the rates of recovery of the various functions—first, recovery of vision with loss of the central scotoma, then recovery of accommodation almost to normal, and, last, partial return of pupillary reactions to light and in convergence-accommodation. The second finding is the persistent response to 2.5% methacholine.

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It would seem necessary to postulate the existence of two lesions in this case: one in the optic nerve, and the other, as suggested by the pupillary response to 2.5% methacholine, in the ciliary ganglion or the postganglionic fibers—similar to the tonic pupil (Adie's syndrome), as pointed out by Scheie.[4]

The presence of the central scotoma, with complete paralysis of pupillary response both to light and in accommodation-convergence, speak against this being Adie's syndrome. Furthermore, at the present time, the pupillary response to light is brisk, not the slow response to continued light stimulus of the typical tonic pupil. Also, the patient, to her knowledge, had never had a dilated pupil prior to the onset of the present illness.

Opticociliary neuritis has been reported with multiple sclerosis and botulism. Rieger [3] felt that his two patients had an acute ciliary ganglionitis due to focal infection, with extension of the inflammatory reaction from the ciliary ganglion to the adjacent optic nerve.

In the present case, there have been no clues to the etiology or associated neurologic deficit except for the absence of the Achilles reflex and, at one time, the questionable weakness of the right arm.

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Annual Reviews

THE ORBIT

A Review of the Literature for 1954

ARTHUR GERARD DEVOE, M.D., New York

SINCE the last review in this field [1] a considerable amount of material related to the diseases of the orbit has been published. This report continues the review to March 1, 1955. There are included, in addition, a number of references published in 1952 and 1953 which were not available for the last publication.

The subject has been relatively static, there being little evidence of basic research in fundamental physiology, such as, for example, has been occurring with glaucoma. The chief exception to this is in the field of endocrine relation to exophthalmos. Even here, however, during the past year there is relatively little which is new. As in previous years, therefore, much of the published material takes the form of individual case reports of isolated rarities.

ANATOMY

Of interest to anthropologists is a paper by Jöhr [2] which describes variations in skull measurements. Two hundred subjects from Western Switzerland were measured to establish upper and lower limits of normal, as well as median, figures for the following: (1) the maximal circumference of the head, (2) the maximal anterior-posterior diameter of the head, (3) the maximal transverse diameter of the head, (4) the distance between the internal canthi, (5) the distance between the external canthi, (6) the distance between the lacrimal puncta, and (7) the distance between the medial edges of the corneas. The author suggests that since it is at times difficult to separate the normal from the abnormal in some malformations about the orbital region, as, for example, in hypertelorism and blepharophimosis, such a set of figures would be useful. It would seem to the reviewer that the measurements could be valuable to physicians and anthropologists examining that specific population group, but that they would not necessarily be valid for mixtures of other racial stocks.

A paper [3] describing in detail variations in the infraorbital foramina of primates has appeared. Of more clinical interest is Scott's [4] description of the growth and development of bones of the face. In general, skeletal growth takes place in two ways: 1. By deposition of bone on the surface of cartilage beneath a perichondrium, followed by deposition of new bone on the older, osseous surface. This is known as surface accretion. In some cases, particularly in membranous bone, earliest calcification is laid down in an area of mesodermal condensation in which there is no cartilage. 2. By replacement of growing cartilage with bone. This is known as endochondral ossification. The facial elements increase in size, alter their form, and become stronger by coordinated deposition and resorption of calcium. Development of the face falls into two phases: 1. From birth to about the seventh year growth is apparently regulated by the cartilage of the nasal septum, cranial base, and mandibular condyle. Growth around the orbits takes place at the sutures as they are separated by growing nasal septum cartilage and orbital content. 2. After the seventh year growth of the nasal septum and at the facial sutures ceases; the orbit is near its adult size. From this time on development is chiefly by surface accretion and internal reconstruction. Growth is not simultaneous and equal throughout the entire

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From the Department of Ophthalmology, New York University Postgraduate School of Medicine.

face and skull. Various regions develop independently and at different periods.

Anatomical and physiological points concerning the lacrimal gland are described by Nover and Müller,[5] using the Hotchkiss-McManus method. Mucopolysaccharides were visualized in the terminal part of the lacrimal gland of adults, extending as far as the lumina of the acini. The efferent ducts were Hotchkiss-negative. The presence of fat in glandular epithelium and of lipoid substances in epithelial cells of adults and infants was confirmed, as was the presence of lymphatic tissue in adults. The lacrimal gland in infants produces mucus, whereas in the adult it produces an aqueous fluid.

DIAGNOSTIC METHODS AND INSTRUMENTATION

It is apparent that keener interest is being taken in the technique of diagnostic radiography of the eyeball and orbit. Reports appear from countries throughout the world discussing techniques and projections to best demonstrate orbital structures.* The importance of the "temporal line" (linea innominata) is described by Drexler,[12] who examined films of the greater wing of the sphenoid and the orbital temporal wall in 280 skulls. The existence of this line is explained as a tangential projection of the condensed bony substance which curves into the temporal fossa. Its constant lower point is the infratemporal spine of the greater wing of the sphenoid.

The use of orbital tomography, particularly when combined with air injection, has its staunch supporters,† but greater interest seems to be centered in the use of contrast media, injected either into the vascular system of the orbit ‡ or, directly, into Tenon's capsule [19] and retrobulbar orbital fat.§ Koenig [22] warns that the retrobulbar injection of the radiopaque substance "Nosydrast" is not entirely harmless and should be used only if the usual clinical methods have failed. He mentions one case of blindness following such orbitography. The possibility of idiosyncrasy to any of these drugs must be constantly kept in mind. Cases of sudden death during cerebral angiography still appear.

A new model exophthalmometer, based on the principles of the Hertel instrument, is being manufactured in Spain.[23]

Use is being made of orbitonometry, employing some modification of the instrument of Copper. Grossman and Burns [24] state that Copper has made some 900 measurements without ill effect. In two cases there were momentary signs of fainting. Recognized contraindications to the use of the method are (1) active conjunctival and corneal disease, (2) corneal insensibility, (3) staphyloma, (4) scleromalacia, (5) intraocular hemorrhage, (6) vascular retinopathy, and (7) detached retina. It is probably wise also to avoid its use in patients with high myopia, those with suspicious evidence of peripheral chorioretinitis, and persons over the age of 50 who have more than the average degree of retinal arteriosclerosis. It is considered possible that compression of the globe might occlude an already sclerotic vessel. The authors conclude that orbitonometry provides assistance in differentiating between the exophthalmos of thyrotoxicosis and that of the thyrotropic phase. This conclusion might be questioned in view of the increasing tendency to discard such differentiation of exophthalmos and to consider the two as different manifestations of the same condition. The technique of using the instrument is to add 100 gm. to the plunger for three seconds, then 200 gm. for three seconds, followed by 300 gm. for two seconds and 400 gm. for two seconds. The readings are then plotted as a graph.

Galindez Iglesias [25] has found patients intolerant of pressures exceeding 300 gm. The statement that a marked difference exists in orbitonometric measurements when exophthalmos is due to vascular, as opposed to neoplastic, conditions seems logical,[26] but its use in differentiating the exophthalmos of

* References 6 through 11.

† References 13 through 15.

‡ References 16 through 18.

§ References 20 through 22.

Graves' disease from that of an orbital tumor [27] seems hazardous.

CONGENITAL AND DEVELOPMENTAL ANOMALIES

Numerous case reports and several comprehensive reviews of developmental disturbances have appeared. The hereditary nature of many of these conditions [28] is emphasized, but it has been noted [29] that both exogenous forces and endogenous mutations can cause identical defects. Of interest is Hicks'[30] work with low doses of x-rays to pregnant rats. A fairly reproducible series of malformations was obtained which could be correlated approximately with the time of injury. For example, irradiation on the 9th day of gestation produced anencephaly, whereas on the 10th day anophthalmos alone was produced. On the 11th to the 12th day other brain deformities occurred, and from the 11th to the 13th day spinal anomalies appeared. It was noted that at certain times specific cells have the capacity for repair, without producing later faulty development. Injury acquired before or after this time does produce permanent change. It seems that cells which are proliferating locally are relatively resistant to injury, whereas those which are at the moment differentiating to form a new structure are the ones most liable to be damaged. This work might well be correlated with the eye changes which occur in infants whose mothers have had exanthematous diseases during the first trimester of pregnancy. As Stockard pointed out many years ago, the same developmental defect may occur after numerous types of injury. Law [31] observes that mild degrees of facial asymmetry are quite common. Some of these he has attributed to variations in uterine position rather than to hazards of childbirth. Changes in the facial skeleton may occur along with cataract and other anomalies in children whose mothers had measles (rubeola) at the appropriate time.[32]

Reports of anophthalmos and microphthalmos ‖ are noted.

The somewhat confusing group of dysostoses involving the bones of the face, as well as, at times, other skeletal structures, usually with a hereditary tendency, continues to be the subject of numerous case reports and reviews of the literature. Because of the many synonyms and eponymic designations, it might be worth while to classify these briefly.

Mandibulofacial dysostosis, referred to commonly in the literature as the Treacher Collins, or Franceschetti, syndrome, is thought to be due to an inhibitory process in the first branchial arch, beginning at the sixth or seventh week of embryonic life. It may occur in the complete form bilaterally or in any number of intermediary, atypical, or unilateral forms. In the complete form the following abnormalities may be found: (1) anti-Mongoloid obliquity of the palpebral aperture with a coloboma in the upper and lower lids at the junction of the inner two-thirds with the outer third of the lid; (2) underdevelopment of the maxilla, zygoma, and mandible; (3) a large, wide mouth with arched palate and abnormal teeth; (4) deformity and malformation of the external, middle, and inner ears; (5) blind fistulae between the angles of the mouth and the ears, and (6) abnormal downgrowth of the hairline onto the cheek.

As Franceschetti has pointed out, the complete form of the disease is not common; it may appear as an imperfect type, in which the anti-Mongoloid shape of the lids and hypoplasia of the facial bones exist but the auricles of the ear remain normal.

In the abortive form, malformations of the lids and colobomata may occur in such minor degrees as to be nearly physiological. They may occur unilaterally. Atypical forms have been described in which one of the principal characteristics is missing and some other malformation, not usually found in the Franceschetti syndrome, is present. Hereditary transmission is irregularly dominant. A number of reports of typical, atypical, and incomplete forms of the disease are to be found in the recent literature.¶ François

‖ References 33 through 39.

¶ References 40 through 48.

has recommended that the term "syndrome of the first branchial arch" be used to cover those cases of typical and atypical mandibular dysostoses that maintain as a common sign aplasia of the mandible. He described families presenting various manifestations.[54] He also pointed out that various colobomatous anomalies of the eye, ranging from unilateral coloboma of the iris to bilateral anophthalmos, may be associated with the syndrome of the first branchial arch.

The second major grouping of these conditions is characterized by premature ossification of the suture lines of the skull and face. The underlying mechanism is unknown, but there is abnormal development of the facial bones themselves, which may relate this group to the first group of mandibular facial dysostoses.

While visual defects are not the rule in Franceschetti's syndrome, pressure effects produced by premature closure of sutures may seriously interfere with vision.

The craniofacial dysostoses include numerous forms of oxycephaly, hypertelorism, and the type which is most familiar to ophthalmologists as Crouzon's disease, a number of reports of which have appeared this past year.# The chief clinical differentiation of Crouzon's disease is the prominent brow, parrot-like nose, small maxilla, and marked protrusion of the lower jaw. The condition is quite obvious in the first few months of life and is of a dominant hereditary character. Association with syndactyly and other skeletal defects has been noted.

Osteopetrosis, commonly known as the Albers-Schönberg disease, or marble bones, is of hereditary tendency and unknown origin. As was pointed out earlier, normal bone growth involves the correlated deposition and absorption of bone in order to secure its enlargement and change of shape. This particular disease is characterized by a failure in the resorbing mechanism, so that bone becomes increasingly dense and large. The orbit is not uncommonly so affected, as is the optic canal, the latter being the cause of its importance to ophthalmologists.*

Polyostotic fibrous dysplasia (osteitis fibrosa cystica, also known as Albright's syndrome) has been reported several times.† It is not common. Its chief pathophysiological component is a disturbance in the undifferentiated cells of the bone-forming mesenchyme, which results in the medullary cavity being filled by connective tissue. The bone then widens; its cortex becomes thin and is replaced by solid connective tissue. Bones usually affected are the skull, in which the orbit may be distorted, and the tibia, upper femur, metatarsals, metacarpals, phalanges, and pelvis. Systemic symptoms, in addition to skeletal lesions, which may cause spontaneous fractures and facial asymmetry with proptosis, are a brown pigmentation of the skin, usually in the area of bone involvement, and endocrine disorders, particularly in girls, manifested by precocious sexual development.

Lipochondrodystrophy (gargoylism; Hurler's disease), a condition of unknown origin, is characterized by fatty infiltration of many body tissues, chondrodystrophy, and dwarfism. Pou and Rodeck[73] described 23 cases in which autopsy was performed. An unknown substance, thought to be a polysaccharide, was demonstrated in various organs. The authors point out that, in addition to the juvenile form, more commonly encountered, there is a late form, which can be confused with Morquio's disease. The latter is a hereditary form of osteochondrodystrophy which produces dwarfing, large head, depressed nose, and widely spaced orbits but does not show the lipoid deposition of Hurler's syndrome. Apparently the diagnosis can most satisfactorily be made by examination of the cornea, which in Hurler's disease becomes cloudy because of lipoid infiltration. Interestingly, the authors add the report of a case in which the corneal disturbance disappeared after treatment with cortisone. In some cases, however, corneal changes are not always present. Although they have been detected at birth, they usually

References 49 through 60.

* References 61 through 64.

† References 65 through 72.

do not develop before the sixth month. Liessens [74] has recently reviewed the literature extensively and, in addition to reporting a case, has noted the difficulty which may be encountered in differentiating the delayed form of Hurler's disease from Morquio's syndrome. He feels that the delayed form may be an intermediate phase between Morquio's syndrome, which has no nervous symptoms, and the precocious form of gargoylism. The subject is reviewed and additional cases are reported by other authors.‡

An unusual case of unilateral exophthalmos is described, the cause of which was a congenital neuroepithelial cyst of the optic nerve.[77]

INFLAMMATION

The occurrence of osteomyelitis in the superior maxilla in infants has again been called to our attention.§ Bonnet [78] has seen 15 infants in the past 26 years in whom this condition has occurred. It is almost exclusively a disease of the first year of life but has occurred in one child of 4 years. He thinks it may be commoner than is realized and may be overlooked in children dying of septicemia. Since the maxillary sinus is not developed at birth, sinusitis is not a precipitating cause. The author believes that the infection may arise from the umbilicus or from local infection around a dental follicle, but more frequently may occur as a transient bacteremia of intestinal origin. The condition should be suspected in a case of one-sided facial swelling with signs of orbital cellulitis. Prompt administration of antibiotics is indicated. Death is now infrequent. Infants who recover from the condition usually do not show changes in the eyeball, but faulty development of the orbit and teeth is to be expected.

Three additional cases of orbital cellulitis in children are available.[80] Lanning believes that 70% of these cases originate from paranasal sinuses. The ethmoid cells are the commonest source, since they are the first to develop; the maxillary sinus is second. After the age of 9 to 10 years the frontal sinus becomes important. Infection is thought to be transmitted in the usual manner, either directly through the thin walls, as an extension of thrombophlebitis, or as an indirect metastasis of organisms. Dental, lid, and face infections are also cited as possible sites of origin.

A case of apex-of-the-orbit syndrome due to periostitis is noted.[81] Treatment with antibiotics was curative.

Handousa [82] observes that amyloid degeneration used to be rather common in cases of prolonged toxic states but is rarely found at the present time. He cites an instance of an inflammatory mass in the orbit with proptosis of 13 months' duration. Upon biopsy this proved to be only amyloid degeneration. Another report [83] suggests that inflammatory response in adipose tissue of an orbit originated from irritation produced by liberated fatty acids from a degenerative dermoid cyst. Although mucormycotic infections have been reported in the eye, a rather unusual situation is described [84] in a 2½-month-old child who had severe involvement of the central nervous system. The left internal carotid artery became thrombosed, and the process extended into the left ophthalmic artery. The entire contents of the orbit and globe became necrotic, and death followed.

Again, the classification of pseudotumor of the orbit is unsatisfactory. A number of cases have been placed on record.‖ Successful results have been described following radiotherapy,[89] repeated retrobulbar injections of 75 units of hyaluronidase, and orbitotomy.[90] Success with the last measure is contrary to the findings of most surgeons, who believe that once the diagnosis is established surgical intervention is unwise, because the inflammatory process is apt to be increased rather than relieved. It is at times necessary, however,[92] to perform a biopsy in order to establish a diagnosis. The reviewer has seen several such patients whose condition apparently was not made worse by surgical intervention.

‡ References 75 and 76.

§ References 78 and 79.

‖ References 85 through 94.

As noted in last year's review, purulent inflammatory processes in the orbit have become something of a rarity because of the effectiveness with which antibiotics control the primary sites of infection. Such disease in the orbit is always secondary.

RELATION OF PARANASAL SINUSES AND TEETH TO OCULAR DISEASE

The importance of paranasal sinusitis as a cause of orbital infection is widely recognized,¶ but the role of these sinuses and the teeth as foci of infection in such nonspecific conditions as keratitis, choroiditis, and optic neuritis seems to be no closer to solution than it was a year ago. The most controversial point, the relation of nasal and sinus pathology to the acute keratitis which follows corneal transplantation at about the third week, can only be answered when those surgeons who do the great bulk of corneal operations are able to make careful and controlled studies. It is the reviewer's belief that although dramatic subsidence of such keratitis may follow shortly upon nasal surgery, it has not yet been demonstrated that this is not a nonspecific response, which could equally as well be obtained by large intravenous doses of adrenal corticosteroids.

Among the numerous reports of mucoceles causing proptosis of the globe, there are several # describing mucoceles arising from the maxillary antrum and displacing the globe upward. These are uncommon; the majority of mucoceles arise from the frontal and ethmoidal sinuses.

Craig [98] reminds us that pain from the frontal or anterior ethmoid sinuses usually is localized in the eye, but pain from the posterior ethmoids is apt to occur in the occipital region. Pain originating from the sphenoid sinus usually is also occipital. Pain from the maxillary sinus is localized around the eye and periorbital area. Treatment for chronic sinusitis is still not very rewarding. Antibiotics and surgery are of relatively little use. Search for allergies should be made.

When a mucocele has been demonstrated by clinical and radiological evidence, its treatment involves complete removal of the cyst and its content. A permanent opening should be made into the nose as part of the surgical removal of all mucoceles. This means that most ophthalmologists are not qualified for such a surgical procedure unless they have received a certain amount of training in that particular field. This, again, is an area in which the combined endeavors of two surgeons may be helpful; the diagnosis cannot always be perfectly established prior to operation. Smith [104] observes that ocular signs and symptoms may be much more important in diagnosis than are nasal symptoms and rhinoscopy.

The role of dental infection as a cause of eye disease is perhaps even more obscure than that of sinus infection.*

Six unusual cases of orbitonasomeningoencephalocele are reviewed by Lasierra.[108] These cysts were rather large and are important in reminding us that the condition is an ever-present possibility in cases of exophthalmos with displacement of the globe, particularly in young persons. Of these six cases, five were treated surgically, with three deaths. The author feels that the prognosis is better when the child is older and suggests that operative intervention should not be done under the age of one year.

INJURIES

The most important publication dealing with orbital injuries is Volume VI of Duke-Elder's "Text-Book," [109] which offers in his usual manner concise and complete information concerning birth injuries to the ocular adnexa, contused injuries to the orbit, fractures, pseudotumors from orbital hemorrhage, perforating wounds of the adnexa with sharp and blunt objects, and foreign bodies in the orbit.

Reports on the management of fractures in and about the orbit continue to be a major source of interest. The treatment of such injuries is becoming standardized. Rowe [110]

¶ References 95 through 105.

References 98, 102, and 105.

* References 106 and 107.

reviews the basic principles involved. They are as follows: 1. Preservation of life. This implies maintenance of the airway by removing blood clots and foreign bodies and observations for edema of the tongue, soft palate, larynx, and floor of the mouth. Hemorrhage must be arrested and shock prevented. 2. Prevention of infection—1500 units of tetanus antitoxin is given immediately, as is 1,000,000 units of penicillin. In addition, 500,000 units of penicillin is given twice a day for five days. 3. Elimination of pain and discomfort. This is accomplished by early fixation of fragments and by the use of proper analgesics. There is general agreement that late reposition of malar bone fractures is difficult and that repair should be as early as possible. Hilger and associates [111] point out that the facial skeleton does not lend itself well to late adjustment or secondary revision and that primary soft-tissue repair is not as vital as is the primary skeletal repair. If possible, it is desirable to accomplish the bony realignment within seven to eight days. Most authors † have advocated standard methods of repair. This ordinarily means the Gillies approach to fracture displacement of the zygoma, the Caldwell-Luc approach, with packing of the antrum for depression of the orbital floor, and, when necessary, interosseous wiring of the fragments under open reduction.

The importance of careful observation following penetrating orbital and transorbital stab wounds is reemphasized. Insignificant external injuries may mask severe neurological complications.‡

Conservative treatment of orbital injuries is recommended [120] on the grounds that edema and hemorrhage in the relatively closed orbital cavity may exaggerate the gravity of early signs. In this respect, it is interesting to note the paper of Hopen [121] concerning subconjunctival and intravenous use of trypsin to produce rapid reduction of acute local inflammation regardless of etiology. Two and one-half milligrams of trypsin in sesame oil can be given intragluteally twice a day for six days. Theoretically trypsin activates a series of naturally occurring enzymes which cause rapid suppression of the signs and symptoms of acute inflammation. Side-effects of pain and induration at the site of injection have been noted in 5% to 15% of patients. Evaluation must await further reports.

Verbiest [122] notes that pulsating exophthalmos after injury is usually due to an arteriovenous aneurysm, but describes two cases in which injury caused fracture of an eroded orbital roof, with expansion of brain into the orbit. Both patients had chronic hydrocephaly. The condition may resemble arteriovenous aneurysm in that the pulsation decreases on compression of the carotid and chemosis and palpebral edema may be present. It may differ in the following respects: 1. A vascular thrill or murmur may be lacking; (2) protruding brain may be palpated through the upper lid; (3) exophthalmos may decrease after ventricular tap, (4) an x-ray may show a bony defect, and (5) ventriculography may clearly outline the pathology. When the intracranial pressure has been reduced, plastic repair of the orbit is done.

Several unusual injuries are reported; in one case [123] a large piece of wood entered the orbit between the lids without damaging the bones, sinuses, or globe. It was extracted and the eye, which was uninjured, reappeared. In another,[124] a piece of metal 6 cm. long was retained for five weeks unsuspected in the orbit and anterior cranial fossa, until an x-ray was taken. It was later removed by the Krönlein approach. In a similar injury,[125] a frontal cranial flap was required to remove a large piece of wood which had been driven through the roof of the orbit.

VASCULAR CONDITIONS

As in previous years, the commonest orbital complication of vascular origin is proptosis associated with arteriovenous aneurysms, specifically of the carotid artery and cavernous sinus. Ordinarily, there is an associated head injury, but the trauma may be slight and occurrence of proptosis delayed.[126] A number of cases of carotid artery-cavernous

† References 112 through 117.

‡ References 118 and 119.

sinus communication are recorded,§ several of which have unusual features. Temler's [127] patient is the fifth recorded person with carotid artery-cavernous sinus fistula who had typical signs on the contralateral side only. The lesion was verified at autopsy. The case is explained by the fact that intercavernous sinus communications are known to exist and that pulsating exophthalmos could be absent on the homolateral side when an injured or a dilated internal carotid artery blocks the egress of blood from the cavernous sinus or when there occurs thrombosis of the ophthalmic vein leading from the sinus.

Bonamour [132] observed optic atrophy with cupping develop in an eye in which 10 years previously pulsating exophthalmos associated with an arteriovenous aneurysm had been successfully treated by ligation of the internal carotid artery. He believed that the atrophy was associated with derangement in the blood supply to the nerve itself, due both to the aneurysm and to the operative procedure.

The usual prognosis for treated carotid-cavernous fistulae has been stated as 12% cured, 30% improved, and 6% dead, the remaining patients being unimproved. Potter,[129] in a short series of 15 cases, states that 5 were cured by nonoperative measures. He thinks this result may have been due to hypotension induced by prolonged rest and by carotid angiography. The suggestion is made that it is possible for angiography to promote thrombosis and that it is better to keep patients under observation for as long as eight or nine months before undertaking surgery.

That angiography is not entirely harmless is indicated by a patient in whom Jamieson[133] actually observed the rupture of an aneurysm by x-ray during the procedure. He states that a new nonirritant, a radiopaque dye, is needed. In spite of potential dangers, however, angiography should not be discarded. In many instances it gives important information obtainable in no other way.

A rather unusual case is reported,[134] the symptoms of which, pain in and about the left orbit, ptosis, total ophthalmoplegia, and vomiting, suggested an intracavernous-carotid aneurysm. No such lesion was found in the operating room. At autopsy, however, a severe periarteritis was observed in the area of the carotid siphon.

Several cases of orbital varices‖ have been recorded. The symptoms included recurring exophthalmos, which occurred when the patient bent over, compressed the jugular vein, or blew his nose.

Cavernous sinus thrombosis is an entity now rarely encountered. Bennett [137] relates the history of a fulminating fatal infection, probably arising from nasal and sinus infection, caused by a hemolytic Streptococcus which failed to respond to antibiotics.

MANIFESTATIONS OF GENERAL DISEASES

A list of all possible causes of exophthalmos would include a number of general, as well as purely local, conditions.[138] Tuberculomas,¶ as well as gummas,# have long been known to cause exophthalmos, and additional cases are recorded. One case [143] of luxation of the eyeball was thought to be associated with excess fatty tissue deposition within the orbit. Bennett [144] reports a rather unique case of rhythmical periodic unilateral exophthalmos of three years' duration in a 45-year-old man. This occurred at about 30-day intervals, apparently having its onset originally with an episode of nausea, vomiting, diarrhea, and low-grade fever. Extensive medical investigation was carried out, without any detectable cause being ascertained. An eosinophilia of 10% to 20% was noted, but no evidence of parasites was found. It was observed that the attacks could be controlled and prevented by systemic cortisone, but that when this was stopped the periodic recurrence of exophthalmos returned.

Although not common in this country, parasitic diseases are a well-recognized cause of exophthalmos in tropical areas. Hydatid cysts of the orbit seem not infrequent,* 32

§ References 127 through 133.

‖ References 135 and 136.

¶ References 139 and 140.

References 141 and 142.

* References 145 through 148.

having been seen in a 25-year period at the ophthalmological clinic at Algiers. Eighty per cent of human infections occurred below the age of 40 years. The presenting signs and symptoms are usually pain, diplopia, and exophthalmos, the last being progressive and unilateral. The localization of the cysts may vary, but they tend to appear between the globe and the orbital wall. At times transillumination may be helpful in making the diagnosis. The only effective treatment is surgical removal of the cyst, but all authors recognize the serious result if the cyst is ruptured during its removal. This seems to take the form of an anaphylactoid reaction. Panophthalmitis, with loss of the globe, followed the rupture of one such cyst.[148] Removal may require a Krönlein approach to the orbit. An untreated cyst usually eventuates in blindness, perhaps from mechanical proptosis of the globe with exposure keratitis. A severe toxic reaction may occur spontaneously, due to small fissures in the cyst or, more commonly, may follow surgical puncture of the cyst. Allergic reactions, to the point of shock, have occurred.

An orbital mass has been removed in a patient with filariasis.[149] Histological examination showed only a chronic granuloma with many eosinophiles. No organisms were demonstrated.

We are reminded † that edema, progressing even to the stage of exophthalmos, can be a sign of trichinosis. The onset is usually acute, however, and is accompanied by much pain upon movement of the eyes and by headache and general discomfort. Eosinophilia may be marked, and in one ocular case the count was recorded as 70%. Cortisone or corticotropin makes the patient feel much better and alleviates the acute phase.

Infectious mononucleosis may cause periorbital and retro-orbital pain.[152]

Toxoplasmosis is not usually considered a probable cause of exophthalmos, but Launay [153] and his collaborators report considerable monocular proptosis in a 6-week-old infant with typical cerebral and ocular involvement of the disease. The exophthalmos remained unchanged during a five-month period that the child was under observation.

Bilateral exophthalmos was the first sign of systemic disturbance in three cases reported by Nover and Goebel.[154] One patient proved to have Hand-Schüller-Christian disease, and the other two, giant-follicle lymphomata.

EXOPHTHALMOS OF THYROID DISEASE

In the last year's "Annual Review" the current concept concerning the mechanism of the production of exophthalmos in hyperthyroidism was summarized. Nothing has appeared during the past year which basically alters these principles. Interest in the subject is attested by articles which have appeared in journals of various specialties throughout the world with the object of summarizing and clarifying present knowledge.‡

Smelser and Ozanics § have continued their investigation of the exophthalmos-producing principles in pituitary extracts, although it has been impossible to obtain completely pure anterior pituitary preparations. They were able to inject relatively pure products of growth hormone, prolactin (Luteotrophin), corticotropin, and gonadotropin. None of these when injected alone caused exophthalmos, edema, increase in orbital fat, or hypertrophy of the Harderian gland, which is the usual response in the guinea pig.

Certain facts seem established in the guinea pig: 1. Crude pituitary extracts containing a mixture of well-defined pituitary hormones produce exophthalmos in thyroidectomized animals, the degree of which varies with the quantity of the pituitary extract given. 2. Gonadotropin, follicle-stimulating hormones, corticotropin, prolactin, and growth hormone do not cause exophthalmos when injected separately. 3. The exophthalmos-producing power of hypophyseal extracts of various species is not strictly proportional to its thyrotropic hormone content, since prepara-

† References 150 and 151. Bassen, E., in discussion on Gould,[151] pp. 646-647. Brown, H. W., in discussion on Gould,[151] p. 646.

‡ References 155 through 176.

§ References 177 and 178.

tions of equal exophthalmos-producing powers may contain as little as 1% of the thyrotropic activity of the other. 4. Injections of combinations of hormone preparations produce exophthalmos, whereas the preparations separately fail to do so. 5. The administration of corticotropin with small quantities of pituitary extract produce marked exophthalmos, whereas little effect is produced when these substances are injected separately. It was therefore concluded that exophthalmos resulted from the synergistic action of two or more substances. The authors were able to demonstrate that corticotropin or cortisone was a potentiating factor in the production of exophthalmos, although the mechanism by which this occurred was not established. At the present time it seems likely that exophthalmos is produced by the interaction of thyroid-stimulating hormone, a steroid hormone from the adrenal gland, and some as yet unidentified pituitary factor.

Dobyns and Wilson [179] have demonstrated an exophthalmos-producing substance in the serum of six women with severe or progressive exophthalmos.

Orbital tissue removed from a patient with malignant exophthalmos [180] was studied histologically and biochemically. A pronounced absolute increase in bulk was observed to be almost wholly due to enlargement of the extrinsic muscles, which were swollen and degenerate but without increase in the number of fibers. There was increase in connective tissue, but no actual edema of the muscle. From the differing reports concerning the actual histology of orbital tissue in various species of animals, it becomes apparent that identical mechanisms may not hold for all species. It is possible that the specific exophthalmos produced in the guinea pig by the use of allyl formate, the histological picture of which is one of edema, and which can be inhibited by an antihistamine, probably has no relation to thyroid disease.[181] Ludwig [182] showed that placing guinea pigs on an ascorbutic diet, which would interfere with the formation of collagen, does not interfere with development of the exophthalmos which follows administration of thyroid-stimulating hormone to the thyroidectomized guinea pig. Vitamin C deprivation does not interfere with the capacity to produce amorphous interfibrillar ground substance.

Aterman [183] produced endocrine exophthalmos in guinea pigs and then injected hyaluronidase retrobulbarly. A measurable protrusion of the eye appeared after a short waiting period, which rapidly reached a maximum and then gradually subsided to below normal. It was believed that this was due to a stage of depolymerization, which produced an increase in water-binding capacity. This, in combination with increased permeability of the capillaries, would produce exophthalmos. When the enzyme was inactivated, the substrate was restored and the eye returned to normal position.

Day and Werner [184] considered the possibility of venous stasis as a cause of exophthalmos in the human being. They injected radioactive sodium into the orbital fat in normal, hyperthyroid, and hypothyroid subjects and noted the rate of removal of the sodium. They concluded that venous obstruction was not responsible for edema or proptosis and suggested the possibility of active inflammation with arteriolar dilation and increased capillary permeability as the responsible mechanism.

An attempt [185] to correlate pretibial myxedema with malignant exophthalmos was not productive. Similarly, an attempt to demonstrate a relationship between hypercementosis or excessive deposition of cement about the teeth [186] does not seem to offer much likelihood of assisting in the clinical evaluation of exophthalmos.

The rather unusual occurrence of congenital goiter and exophthalmos in an infant born of a mother in the hypothyroid state with pronounced exophthalmos is reported.[187] There is only one previous report of congenital hyperthyroidism. Because of the hypothyroid state of the mother, the hyperthyroid state of the child is explained on the basis of stimulation of the fetal thyroid by excessive maternal thyrotropic hormone. The infant responded well to strong iodine solution U. S. P.

Although the number of patients with exophthalmos of hyperthyroid disease who lose visual acuity is relatively small, Igersheimer [188] reports six such cases, in five of which blindness seemed imminent. All had a central or paracentral scotoma and, although the discs were normal in three patients, there seemed no doubt that the visual failure was due to the involvement of the optic nerve in the orbit behind the globe near or in front of the optic foramen. The usual methods of treatment are described. It is believed that even in severe cases vision can be restored unless there is ophthalmoscopic evidence of nerve damage.

There have been no new developments in treatment. It is recognized that results are poor as far as complete cure with regression of the exophthalmos is concerned, but that the condition can usually be arrested without permanent loss of vision.‖

The use of posterior pituitary injection U. S. P. (Pituitrin) applied locally in the form of a soaked gauze pad upon the eyelids for 15 to 20 minutes hardly seems likely to be of help.[196]

Although radioactive iodine is being employed in the treatment of patients with hyperthyroidism, the tendency [198] is to restrict its use to patients under 45 years of age because of a theoretical possibility of the production of carcinoma of the thyroid gland. It is believed that, although 10 years have elapsed without the production of such a case, another 20 years will be required to answer this question definitively. Its use is preferred in recurrent hyperthyroidism following surgery.

X-irradiation of the pituitary has advocates.¶ Gedda and Lindgren [199] suggested that with severe proptosis of an emergency nature, radiation should first be directed to the orbit to reduce the proptosis immediately and this should be followed by irradiation of the pituitary for its long-term effect. In four patients [200] with malignant exophthalmos the blood thyrotropin levels were followed before, during, and after x-irradiation of the pituitary. Following such therapy the serum level of thyrotropin was constantly decreased, particularly so in patients with the highest blood levels and those with the most recent exophthalmos.

The question of the value of corticotropin and cortisone in malignant exophthalmos continues to produce a division of opinions. Favorable# and unfavorable* reports are available. A statement by a panel appointed by the National Medical Research Council describes 28 patients in whom cortisone and corticotropin were given in the usual doses. It was concluded that no significant benefit was obtained, but that perhaps large enough doses were not used. It was believed that the treatment was worthy of further trial in those patients with acute and sudden onset of the disease and that the least response should be expected in those without edema or chemosis. In the future, higher doses, including intravenous administration of corticotropin, should be considered. Aterman and Greenberg,[208] noting that exophthalmos can be regularly reproduced in rats by administering cortisone, suggest that the thyroid hormone prevents the building up of excess adrenocorticosteroids. The rat apparently behaves differently from the guinea pig. Boas and Scow [209] note that young thyroidectomized rats when treated with cortisone are retarded in the development of the body and skull, but not in the development of the eyes. Hence, such animals have more prominent-appearing eyes because their orbits are smaller and the appearance of exophthalmos can be falsely obtained.

Rather infrequently, surgical measures are still required to protect the globe from exposure. The method of lid mobilization and tarsorrhaphy described by Gartner and Chamlin [210] seems worthy of trial in cases where ordinary lid adhesions do not hold.[211] In addition to the more commonly used methods of decompression, frontal osteotomy

‖ References 189 through 195.

¶ References 197 through 201.

References 202 through 204.

* References 205 through 207.

with removal of the superior and lateral borders of the orbit [212] and decompression into the antrum [197] has been suggested.

Naffziger,[213] in a Hunterian lecture, has reviewed his experience with orbital decompression in 40 cases of malignant exophthalmos due to thyroid disease. He has found no significant relation between the level of the basal metabolic rate and the degree of exophthalmos. He believes that the retro-ocular pressure is more important as a guide to the necessity for decompression than is the extent of ocular protrusion. He feels that it is essential to remove a large section of orbital roof and that there is no need to remove the roof of the optic canal. No deaths or serious complications have been encountered in his series.

TUMORS

Orbital tumors of various types always arouse the interest of the ophthalmic surgeon. Most of the reports continue to be isolated case studies and include fibrosarcomas † and angiomas.‡ Martelli [217] believes that these tumors can pass through various stages of maturity, from a "hyperplastic angioma to a solid endothelioma." Surgical excision is preferred by most authors, although there are occasional reports of the use of radiation therapy. Neurofibromatosis with involvement of the lids and orbit is reported on numerous occasions.§ The presenting appearance can be most pleomorphic, and attention should always be paid to the possibility of diagnostic areas elsewhere in the body, as exemplified by the café-au-lait spots. The tumors are generally benign, although Schiff-Wertheimer reports a malignant tumor in a child, the histological diagnosis of which is probably a malignant neurolemmoma.

Several cholesteatomas ‖ are recorded, as are osteomas,¶ dermoid cysts,[233] and tumors extending from the globe.# The matter of exenteration in these cases will be discussed in the section on surgery.

At birth a retinoblastoma can already be extensively invading the orbit.[236] In less unfavorable cases successful reports have been obtained following radiation treatment. It hardly seems proper to subject these children to medical or surgical procedures in view of the high percentage of metastases.*

Lacrimal gland tumors † form a well-marked group, in which definitive treatment is beginning to crystallize. It is generally agreed that the encapsulated, well-differentiated lesions can be excised with every probability of a favorable course. Less differentiated tumors require exenteration, and in many cases removal of the orbital roof and wall, if cure is to be hoped for. Jones and Pfeiffer [238] have demonstrated the help that may be obtained from the x-ray. It is admitted that x-ray diagnosis is not infallible, since early cases, even of a malignant nature, may show no change. But in general the malignant tumors show an enlarged lacrimal gland fossa with involvement of the bone cortex. There is increased density in the bone adjacent to the gland. An area of hyperostosis, which may be mottled in appearance but is usually homogeneous, follows the growth of tissue cells into the bone. Subsequent irritation of the bone produces the hyperostosis. Davies [239] does not like the term "mixed tumor" and has substituted "pleomorphic adenoma and adenocarcinoma." It is not likely that a universally acceptable terminology will be immediately forthcoming. An unusual localization for a mixed tumor is noted in an eyebrow.[243] Traumatic origin was suspected.

Nonchromaffin paragangliomas [244] are an uncommon group. The term is used to designate a histologically similar group resembling carotid body tumors and arising from poorly

† References 214 through 216.

‡ References 217 through 221.

§ References 222 through 227.

‖ References 228 and 229.

¶ References 230 through 232.

References 234 and 235.

* Reference 237. Rintelen, F., report at a meeting of the Swiss Ophthalmological Society, Oct. 4-5, 1953.

† References 238 through 242.

known carotid-body-like formations, which can be found normally in such sites as the bifurcation of the carotid artery, in or about the middle ear, in the ganglion nodosum of the vagus nerve, and in the region of the aortic arch. The case reported [244] is a multicentric one of 15 years' duration, arising in the neck and invading the orbit. These tumors are usually thought to be benign, but in this particular instance death followed two years after partial surgical excision and radiation therapy. The authors feel that this tumor was a primary lesion arising from the ciliary ganglion, which up to the present has not been reported in the literature.

Case reports of neuroblastoma ‡ are noted.

McGavic's 15-year follow-up § of 20 patients with lymphomatous tumors involving the eye and adnexa is important. It is rather generally agreed that the lymphomatoid diseases are interrelated and can be transitional from one type to another with or without the presence of blood changes. In general, the prognosis is better than has ordinarily been believed. Of importance is the fact that the clinical appearance of the eye, as well as the histological appearance of the tumor, apparently is an unreliable guide as far as the prognosis for the individual patient is concerned. Diamond ‖ states that lymphomatous tumors can be placed in three categories. Category I is unicentric, without blood changes or other alterations; Category II demonstrates early beginning generalization, although still with reasonable localization of the disease; Category III is the universal category into which all patients with leukemia will fall. The choice of therapy in all varieties of lymphoma should be radiation, treatment in general tending to be insufficient. Chemotherapy, e. g., with the nitrogen mustards, cortisone, corticotropin, and anti-folic-acid drugs, is still being investigated.

A number of case reports in the lymphomatoid group are available.¶

Eosinophilic granuloma of the bone has been considered rather rare as far as the orbit is concerned. Five reports appeared in the literature this year. In one,[260] folic-acid antagonists were used. In four months the exophthalmos disappeared. The course during the succeeding six years was one of control while the drugs were used, but of relapse as soon as they were discontinued. Other cases have responded to both surgery and radiotherapy.# The relation of this disease and of other xanthomatous diseases of the orbit [265] to Hand-Schüller-Christian disease or to the Letter-Siwe disease is not entirely clear.

Frequent records of tumors metastatic to the orbit have been encountered. The bulk of these tumors * have arisen from the nasopharyngeal cavity or paranasal sinuses or are bony tumors spreading from the adjacent maxilla and dentigerous areas.†

Meningiomas ‡ not infrequently invade the orbit. In an unusual case,[278] the original diagnosis, made 36 years previously, was "benign osteoma," but the growth was successfully removed at the later date.

Orbital metastases of a Wilms tumor,[281] a malignant melanoma of the leg,[282] and a carcinoma of the breast [283] are described.

Severe pain is not considered a presenting symptom of most orbital tumors, but Croce and Dejean [284] report three such patients whose symptoms resemble those of a tic douloureux. It has also been suggested that orbital pain following malignant tumors can be controlled by alcohol injection of the Gasserian ganglion [285] or by resection of the greater superficial petrosal nerve [286] in extreme cases.

SURGERY

The problem of enucleation and the most effective type of implant has not yet been satisfactorily settled. There is general agree-

‡ References 245 through 248.

§ Reference 249. Diamond, H. D., in discussion on McGavic,[249] pp. 644-645. Merriam, G., in discussion on McGavic,[249] pp. 643-644.

‖ Diamond, in discussion on McGavic,[249] pp. 644-645.

¶ References 250 through 259.

References 261 through 264.

* References 266 through 272.

† References 273 through 277.

‡ References 278 through 280.

ment that some type of implant is desirable, but in recent years the trend is toward the completely buried implant. Modifications of existing implants continue to appear.§ Some of these are difficult to evaluate because no figures are given concerning length of follow-up or number of cases in which the implant is used. Other series are relatively lengthy.

Troutman [294] has given us a five-year survey of magnetic implants and has described the course of 102 such cases, 98 primary and 4 secondary. A one-year follow-up was obtained for 68% of the group and a three-year follow-up for 27%. Extrusion of only 4% of these implants occurred, the figure approximating that for the usual buried spherical implants. Displacement within the orbit does not occur, and uncovering of the implant only rarely. Should such uncovering occur, he urges early immediate closure in the operating room. Discharge has not been a serious problem, and an allergic reaction has occurred in only one case. The major advantages of this type of implant are recorded as (1) the prevention of pressure in the lower cul-de-sac because of the attraction of the prosthesis to the implant posteriorly; (2) a flat anterior surface, which acts as a fulcrum and permits better rotation, and (3) absence of migration of the implant, because of its attachment to the muscles.

The magnetic implant described by Young [293] is an intrascleral one performed after evisceration. The magnetic implant of Tomb and Gearhart has been used in 117 patients since 1949. There have been but two extrusions and only six dehiscences, which have apparently not given serious trouble. Several of these patients have shown post-enucleation sinking of the upper lid, which the authors attribute to postsurgical atrophy of orbital tissue.

An extraconjunctival implant has recently been described [295] and condemned.[296] No figures are given as to the number of cases in which this has been used, or to the length of follow-up; evaluation, therefore, must await further reports.

§ References 287 through 293.

Adding to the almost limitless number of materials used for orbital implant, Pajtas [297] describes 163 patients in whom natural or artificial amber was wrapped in a piece of the patient's own fatty tissue and then implanted. He reports satisfactory, well-healed implants in 90% of the cases. Although the motility of the implant was good, movement was transmitted to the prosthesis in only 50% of the cases.

Additional reports upon the use of plastic sponge material for orbital implants have appeared during the past year.‖ Pearlman [300] has performed this procedure in 60 patients, with follow-ups for as long as 24 months. In 9% of these cases the operation was unsuccessful because of irreparable exposure of the implant base with infection. He states that this exposure may be avoided by attaching the muscles to the anterior face of the implant and that such a series is now being developed. It is of interest to note that plastic surgeons have been employing polyvinyl sponge to restore soft-tissue contour and that the results are not entirely free of complication.¶ Kiskadden points up the warning that has previously been noted in these reviews, namely, the potential hazard of producing cancer by its use. He has advised against the use of such material in plastic procedures on the breast. It is interesting to observe that Streiff [303] believes the German-made plastics to be less apt to cause irritation in the orbit than the American-manufactured ones.

Although enucleation is becoming a less frequently performed surgical procedure, education of the public as far as further treatment of infections is concerned [304] will reduce the number still more. Fuchs [305] urges that particular pains be taken at the operating table to avoid complications. He states that the most serious of these, removal of the wrong eye, has occurred several times, and that particular attention should be paid to marking the eye following ophthalmoscopy, before the patient goes to the operating room.

‖ References 298 through 350.

¶ References 301 and 302.

Techniques of making and fitting artificial eyes # are not yet standardized. Jardon [307] reemphasizes a point which is frequently overlooked. It is many times possible to cover a disfigured globe with a thin, contact-lens type of shell eye and secure a most satisfactory cosmetic appearance.

To overcome troublesome discharge, not uncommonly found in sockets, a streptokinase-streptodornase preparation [308] has been used successfully in two such cases. One ampul of the drug is dissolved in 30 cc. of isotonic saline and the preparation made fresh each day.

Several new instruments for use in orbital surgery have been described: a deep angulated concave retractor,[309] an orbital compressor-aspirator,[310] and a book [311] to be used in effecting reduction of impacted malar bone fractures.

Methods of repairing the lower fornix in the anophthalmic socket [312] and a generally contracted socket,[313] are described. The use of a full-thickness skin graft [313] has justifiably not been popular in this country.

Prosthetic devices [314] to cover badly deformed sockets have their place but are in general not very satisfactory. Although alloplastic materials have been advised in the repair of severe orbital defects,* most plastic surgeons prefer the use of autogenous cartilage [317] or bone.† The paper of Converse and Campbell [319] describes in detail the indications, technique, and complications of bone grafting about the face. The use of preserved cartilage still has its advocates [320] and is probably satisfactory in areas not subject to trauma or weight bearing, such as those involved in repair of a fracture of the orbital floor.

Orbital tumors have been removed by the temporal, or Krönlein, approach ‡ by way of the antrum,[323] and by the subfrontal avenue.[324]

Most ophthalmologists approach exenteration of the orbit with misgivings, not so much because of the technical difficulties of the operative procedure as because of the eventual poor outcome in most of these cases. Surgeons are still hesitant about the proper procedure when, in the course of enucleation of the globe for a malignant melanoma, gross extension of the tumor is found in the orbit.

Two recent papers are helpful.§ Naquin [325] has reviewed 48 exenterations performed in the past 25 years at the Wilmer Institute. Of the nine patients with malignant melanomas with extraocular extension, only one is alive and without recurrence five years after the operation. In Rendahl's series [326] of 20 similar cases 17 died of metastases within two years after the operation. All but one patient with extension of malignant melanoma outside the globe eventually died. From these two series it would seem hardly justified to perform an exenteration once the tumor has appeared in the orbit. In both series, when retinoblastoma had extended beyond the globe into the orbit, exenteration has proved hopeless. In general, exenteration is not indicated in malignant melanomas which have extended beyond the globe or which have recurred after primary removal, in extension of retinoblastoma, and in sarcomas of the orbit in children. The operation is indicated in carcinoma of the skin or conjunctiva which has invaded the orbit and in some types of lacrimal gland tumor. It is the opinion of the reviewer that ophthalmologists as a rule are not radical enough in the treatment of malignant tumors of the orbit. In many of these cases, if cure is hoped for, removal not only of the orbital content, but also of the roof, lateral wall, floor of the orbit, antrum, and ethmoid cavities, is necessary.‖ Treatment of this type is ordinarily beyond the scope of the average ophthalmologist and requires the services of the head and neck surgeon. The ophthalmologist may think that he has carried out an adequate procedure in performing an exenteration,

References 306 and 307.

* References 315 and 316.

† References 318 and 319.

‡ References 321 and 322.

§ References 325 and 326.

‖ References 327 and 328.

whereas he has merely performed ineffectual surgery, which will shorten the patient's life expectancy. It is of paramount importance that the ophthalmologist collaborate with the head and neck surgeon in cases of this type.

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Special Reports

ESTIMATION OF LOSS OF VISUAL EFFICIENCY

The Committee appointed by the Council on Industrial Health, American Medical Association, herewith submits a revision of the "Appraisal of Loss of Visual Efficiency," adopted June 13, 1940, by the House of Delegates of the American Medical Association on recommendation of the Section on Ophthalmology. The aim of this report is to revise the methods of determining the loss of visual efficiency of a person who has suffered visual impairment as a result of disease or injury.

Respectfully submitted,

EDMUND B. SPAETH, *Chairman*
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Approved and accepted by the Executive Committee of the Section on Ophthalmology, American Medical Association, Atlantic City, N. J., June, 1955.

HAROLD G. SCHEIE, M.D., *Secretary*

SECTION I: ESSENTIAL FACTORS IN DETERMINATION OF VISUAL EFFICIENCY

VISUAL efficiency is defined as that degree or percentage of the competence of the eyes to accomplish their physiologic functions, including (1) corrected visual acuity, for distance and near, (2) visual fields, (3) ocular motility with absence of diplopia, and (4) binocular vision. Although these factors do not possess an equal degree of importance, vision is imperfect without the coordinated action of all. Other functions, although secondary and dependent, are recognized as important, such as color perception, adaptation to light or dark, and accommodation. Because these functions are inherently dependent on the status of the previously mentioned four coordinating functions of vision, they are not included in the basic method of calculation of the percentage of loss of visual efficiency.

SECTION II: CENTRAL VISUAL ACUITY

For purposes of standardization, the Snellen test chart utilizing block letters or numbers without serifs, the illiterate E chart, or Landolt's broken-ring chart is desirable. Illumination of the test chart should be at least 5 foot-candles (f-c.), and the chart or reflecting surface should not be dirty or discolored from age. The test distances should be at 20 ft. (6 meters) and at 14 in. (36 cm.). In line with the recommendations of the American Committee on Optics and Visual Physiology, Subcommittee on the Problem of an International Nomenclature for Designating Visual Acuity,[1] the sizes of letters in the test lines form a geometric progression, as proposed by Green in 1867. With this scale, the size of letters of each successive line is 26% larger than that of the following line, or 20% smaller than that of the preceding line. Visual acuity is most commonly recorded in the form of a fraction in which the test distance, in feet or meters, is expressed as the numerator. The denominator represents the distance at which the smallest letters discriminated by the patient would subtend 5 minutes of arc (Table 1). Although this method of designation appears to be a mathematical fraction, it is purely a convenient form of notation by ophthalmologists and does not represent a true percentage of normal visual acuity.

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For designation of visual acuity for near, a similar Snellen ratio can be utilized using inches, or a comparable Jaeger or a point type system may be used, according to Table 2. The visual acuity may also be designated as visual angle, in accordance with the recommendation of the previously mentioned Subcommittee on Nomenclature. A visual angle of 1.0 minute of arc of each constituent part of the test character (or 5 minutes for the entire character) can be discriminated by a "normal" subject.

The best vision obtainable with ophthalmic lenses should be used in determining the degree of central visual acuity. It is realized that the use of contact lenses might further improve vision reduced by irregular astigmatism from corneal disease or injury. However, the practical difficulties of fitting, expense, and tolerance of contact lenses are sufficiently important at the present time to favor recommendation that only regular ophthalmic lenses be used to determine the best corrected vision.

The visual disability due to monocular aphakia (with normal corrected vision in the other eye) varies considerably among different persons because of several factors,

TABLE 1.—*Percentage of Central Visual Efficiency Corresponding to Central Visual Acuity Notations for Distance*

Snellen		Visual Angle, in Minutes *	Per Cent Central Visual Efficiency	Per Cent Loss of Central Vision
English	Metric			
20/16	6/ 5	0.80	100	0
20/20	6/ 6	1.00	100— †	0
20/25	6/ 7.5	1.25	95	5
20/32	6/10	1.6	90	10
20/40	6/12	2.0	85	15
20/50	6/15	2.5	75	25
20/64	6/20	3.2	65	35
20/80	6/24	4.0	60	40
20/100	6/30	5.0	50	50
20/125	6/38	6.3	40	60
20/160	6/48	8.0	30	70
20/200	6/60	10.0	20	80
20/300	6/90	15.0	15	85
20/400	6/120	20.0	10	90
20/800	6/240	40.0	5	95

* Denoting each constituent part of test character. When the visual angle of each constituent part is multiplied by 5, the product is the visual angle of entire test character.

† For purposes of calculation of the per cent of central visual efficiency, 100% is used. This does not consider the fact that the average normal person usually has a visual acuity of 20/16 corrected by ophthalmic lenses.

including age and accommodative power, ability to tolerate a contact lens for adequate periods of time, ability to obtain single binocular vision comfortably when wearing a contact lens, and the importance of binocular vision in the patient's work. If the vision in the aphakic eye can be corrected to 20/20, the disability may be slight in a presbyopic patient who can wear a contact lens comfortably for periods of eight hours or more. However, a young person doing close precision work may be incapacitated for this task even when wearing a contact lens. Other persons may not be able to obtain and wear a contact lens comfortably for long periods of time, for one reason or another. However, even an uncorrected aphakia is not equivalent to a blind eye because of the usefulness of side vision, and the possibility of correction if the normal eye should be injured subsequently. The practice of considering monocular aphakia as the full loss of visual efficiency in one eye does not recognize the value of an eye with no abnormality except the loss of the lens. With these considerations in mind, it is recommended that monocular aphakia be considered as a partial visual disability, viz., 50% of the central visual efficiency of that eye when corrected

by lenses (Table 1). For example, if corrected vision in the aphakic eye is 20/40, the allowable central visual efficiency of that eye would be $0.50 \times 0.85 = 43\%$ or a loss of central vision of 57%.

The visual handicap resulting from aphakia corrected by regular ophthalmic lenses can only be estimated. This factor would be of importance in cases of binocular aphakia, or in monocular aphakia where the corrected vision in the aphakic eye is greatly superior (perhaps 50%) to that of the opposite eye. In such cases where the corrected aphakic vision is used for the patient's activties, it is recommended that this per se be considered an additional partial visual handicap of 25% of the best corrected binocular visual efficiency, as calculated under Section VI. For example, if the binocular visual efficiency of the corrected aphakic patient is 75%, the final estimation of the visual efficiency of that patient would be $0.75 \times 0.75 = 56\%$.

A visual acuity of 20/20 or better (6/6 or better, or visual angle of 0.1 minute or less) is considered 100% acuity for distance vision, and Snellen 14/14, Jaeger 1, or 3-point type (with presbyopic correction if necessary) is considered 100% acuity for near vision (14 in., or 36 cm.). A revision of the estimations of percentage loss

TABLE 2.—*Percentage of Central Visual Efficiency Corresponding to Central Visual Acuity Notations for Near*

Snellen	Jaeger	Point	Visual Angle in Minutes *	Visual Efficiency	Per Cent Loss of Central Vision
14/14	1—	3	1.0	100	0
14/18	2—	4	1.25	100	0
14/22	...	5	1.6	95	5
14/28	3	6	2.0	90	10
14/35	6	8	2.5	50	50
14/45	7—	9+	3.2	40	60
14/56	8	12	4.0	20	80
14/70	11	14	5.0	15	85
14/87	...	..	6.3	10	90
14/112	14—	22	8.0	5	95
14/140	...	..	10.0	2	98

* Denoting each constituent part of test character. When the visual angle of each constituent part is multiplied by 5, the product is the visual angle of the entire test character.

of visual acuity corresponding to the Snellen and visual-angle notations for distance and near is given in Tables 1 and 2. This has been done in the light of statistical reports of average "normal" vision, and experience in the disabilities caused by reduced visual acuity. It should be remarked that no scientific studies are available relating central visual acuity, visual field, and motility deficiencies to the actual performance of various duties. This Committee feels that the table set up by the 1925 and 1940 American Medical Association Committees overestimates the loss of visual efficiency for distance acuities poorer than 20/200 and underestimates the loss for near acuities poorer than 14/28, Jaeger 3, or 6-point type. Although the visual angles may be the same, it should not be concluded that the Snellen notation for distance is the exact equivalent of the Snellen notation for near in respect to visual efficiency because of other influences, such as accommodation, size of retinal image, etc. Also, the visual disability in reading with acuity for near of 14/35 (Jaeger 6 or 8-point type) is far greater than the visual disability for distance with 20/50 vision, which has the same visual angle. The revised Tables 1 and 2 represent an effort to relate more closely visual acuity and visual disability in the light of experience. Because of the importance of good near vision in the performance of

work, the revised Table 2 weights this disability more heavily than the 1940 American Medical Association table. Calculation of the percentage of central visual efficiency for both distance and near vision would therefore be the average of the two percentages.

SECTION III: VISUAL FIELD

The extent of the visual field is determined by the use of the usual perimetric methods, utilizing a white target which subtends a 0.5-degree angle (that is, a 3 mm. white disc at a distance of 330 mm.) under illumination of not less than 7 f-c. A 6 mm. white disc is recommended for uncorrected aphakia. The test object is brought from the peripheral to the seeing area. At least two peripheral visual fields should be obtained which agree within 15 degrees in each meridian. The reliability of the patient's responses should be noted. The result is plotted on an ordinary visual field chart on each of the eight 45-degree principal meridians.

The minimum normal extent of the visual field from the point of fixation can be defined as follows: temporally, 85 degrees; down and temporally, 85 degrees; down,

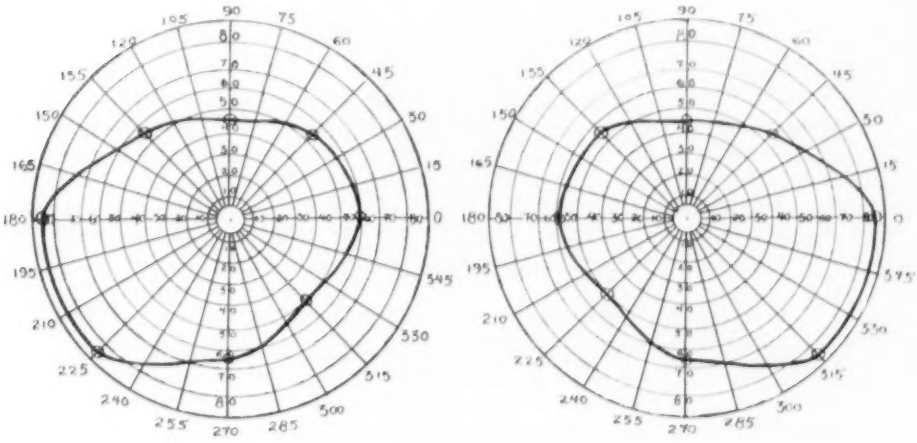

Figure 1

65 degrees; down and nasally, 50 degrees; nasally, 60 degrees; up and nasally, 55 degrees; up, 45 degrees, and up and temporally, 55 degrees (Fig. 1). These figures are about 10 to 15 degrees less than the average normal, thus allowing for poor or delayed subjective responses or undue prominence of the brow or nose.

The visual field efficiency of one eye in percentage is obtained by adding the number of degrees of the eight principal radii given above for the 3/330 white isopter, which normally is 500 degrees, and dividing by 5. For example, if the field is contracted down to 25 degrees in all eight meridians, there would be a remaining visual field efficiency of $25 \times 8 \div 5 = 40\%$, or loss of 60%. If the field is contracted down to 5 degrees in every meridian, the remaining efficiency would be $5 \times 8 \div 5 = 8\%$, or loss of 92%. If the entire temporal field is lost, the loss would amount to

Up and temporally	55
Temporally	85
Down and temporally	85
Average of up and down (½[45+65])	55
	280 ÷ 5 = 56%,

or a remaining efficiency of 44%. If the upper nasal quadrant is lost, the loss of field efficiency would amount to 55+52 (average of up and nasal meridians=45+60 ÷ 2) ÷ 5 = 21%, or a remaining efficiency of 79%. Loss of visual field efficiency can be calculated for other field defects in a similar manner. Although the extent of loss of visual field efficiency cannot be determined accurately for a ring scotoma, an approximation can be obtained by considering the width of the ring scotoma to be equivalent to loss of peripheral visual field. A similar estimation of visual field loss can be applied to enlargement of the blind spot using a 2 mm. white test object at a distance of 1 meter from a tangent screen with the subject wearing his corrective lenses; for example, a general enlargement of the blind spot of 5 degrees would result in a visual field loss of 8×5÷5=8% loss, or 92% visual field efficiency. Because a central scotoma directly affects the central visual acuity, such loss of visual field is not used in the final calculation of the visual efficiency.

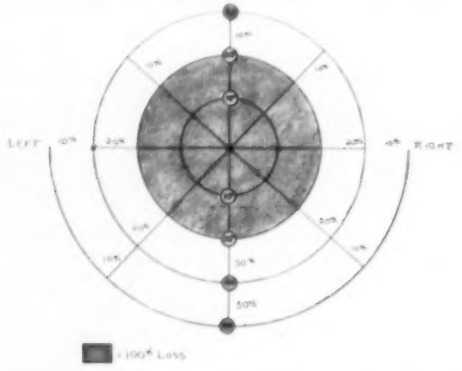

Fig. 2.—Percentage loss of ocular motility of one eye in diplopia fields.

SECTION IV: OCULAR MOTILITY

Visual efficiency is related to the function of extraocular muscles in two major ways: (1) the absence of diplopia, and (2) binocular vision. Except on looking downward, it is doubtful whether diplopia causes significant visual disability unless it is present within 30 degrees of the center of fixation. The extent of the diplopia in the various directions of gaze is determined on the perimeter at 33 cm., or on the ordinary tangent screen at 1 or 2 meters' distance from the patient in each of the 45-degree meridians, utilizing a small test light and without the addition of colored lenses or correcting prisms. The degree of separation of the two lights is plotted along each of the three meridians above for 10, 20, and 30 degrees away from the straight-ahead position and for 10, 20, 30, and 40 degrees away from the straight-ahead position horizontally and below (down and right, down, and down and left) (Fig. 2.). The results of the separation of the two images are plotted on a visual field chart.

The percentage loss of ocular motility efficiency of one eye caused by diplopia in various positions of gaze is given in Figure 2. Diplopia within the central 20 degrees represents a 100% loss of motility efficiency in one eye. If diplopia is not present in the central 20 degrees of ocular rotation from the straight-ahead position, diplopia present on more peripheral gaze should be considered as a loss in motility efficiency

of one eye, according to Figure 2. For example, if there is diplopia only on looking straight down between 20 and 40 degrees, the loss of ocular motility efficiency of one eye is 50+30=80%. Again, if diplopia is present only on looking between 20 and 40 degrees to the right, due to a residual paresis of the right lateral rectus muscle, the loss of ocular motility efficiency of one eye is 20+10=30%.

If the patient has lost binocular vision as a result of disease or injury and, because of suppression, diplopia is not present, the degree of visual disability will depend on how important good depth perception would be for the performance of the patient's work. However, loss of binocular vision without other ocular abnormalities probably does not represent more than a 50% loss of ocular motility efficiency of one eye in the average case. Tests for binocular vision can be made with any of the well-recognized instruments, such as the major amblyoscope and various forms of stereoscopes.

Strabismus following disease or injury as discussed here is considered only on the basis of the loss of motility efficiency. The cosmetic defect of a strabismus is considered to be a separate factor (see Section VII).

SECTION V: CALCULATION OF VISUAL EFFICIENCY OF ONE EYE

Determination of the visual efficiency of one eye considers the average percentage of central visual efficiency for distance and near, percentage of visual field efficiency, and percentage of ocular motility efficiency, including absence of diplopia and binocular vision. For example, with average central visual efficiency for distance and near of 30%, visual field efficiency of 40%, and motor field efficiency of 70%, the total visual efficiency of this eye would be $0.30 \times 0.40 \times 0.70 = 0.84$, or 8.4% of total visual efficiency of this eye. Should the visual efficiency of one eye be reduced to less than 10%, the visual loss is considered to be total from a practical standpoint.

SECTION VI: CALCULATION OF BINOCULAR VISUAL EFFICIENCY

If the vision in one eye is completely lost and the fellow eye is normal, it has been found by common experience that the total visual efficiency of such a person is actually more than 50%. In agreement with the opinion of the previous committee of the American Medical Association in 1940, a more nearly correct estimation of visual efficiency can be obtained by weighting the visual efficiency of the better eye three times according to the following method:

$$\frac{(\%\text{ efficiency better eye} \times 3) + (\%\text{ efficiency worst eye})}{4} = \text{binocular visual efficiency.}$$

For example, the binocular visual efficiency of a patient with one blind and one normal eye would be $\frac{100\% \times 3 + 0\%}{4} = 75\%$, or binocular visual loss of 25%.

When disease or injury has involved both eyes, a loss of efficiency in ocular motility is used only in computing the efficiency of the less efficient of the two eyes. The estimation of the visual efficiency of the better eye is therefore based only on the central visual acuity and the visual field of this eye.

Should the total binocular visual efficiency of the patient be less than 10%, for all practical purposes the patient can be considered blind.

SECTION VII: TYPES OF OCULAR ABNORMALITIES NOT INCLUDED IN THE VISUAL EFFICIENCY FACTORS

Certain types of ocular disturbance are not included in the previously mentioned computations, and these may result in disabilities the value of which cannot be calculated by any scale as yet scientifically determined. Such are disturbances of

accommodation, color vision, light and dark adaptation, metamorphopsia, entropion, ectropion, lagophthalmos, epiphora, strabismus, deformities of the orbit, and cosmetic defects.

SECTION VIII: SOME CONSIDERATIONS IN THE FINAL ESTIMATION OF LOSS OF VISUAL EFFICIENCY

It is recommended that final estimation of visual efficiency be deferred following certain conditions, for example, at least 3 months after all visible evidences of inflammation have disappeared, at least 6 months following surgery, and at least 12, and preferably not more than 16, months in cases of disturbance of the extraocular muscles, sympathetic ophthalmia, traumatic cataract, or optic nerve atrophy.

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VISUAL FIELD DETERMINATION

NAME.....DATE.....

PERCENTAGE OF VISUAL FIELD EFFICIENCY: RIGHT EYE.....LEFT EYE.....

DISTANCE OF EYE FROM PERIMETER.....SIZE OF TARGET.....ILLUMINATION.....

RELIABILITY OF TEST..... EXAMINED BY.....

To Determine Percentage of Visual Field Efficiency

The extent of the visual field is determined by the use of the usual perimetric methods, utilizing a white target which subtends a 0.5° angle (that is, a 3 mm. white object at a distance of 330 mm.) under illumination of not less than 7 foot-candles. A 6 mm. white object is recommended for uncorrected aphakia. The test object is brought from the peripheral to the seeing area. At least two peripheral visual fields should be obtained which agree within 15 degrees in each meridian. The reliability of the subject's responses should be noted. The result is plotted on the visual field charts below on each of the 45° principal meridians. The minimum normal extent of the visual field from the point of fixation can be defined as follows: temporally, 85°; down and temporally, 85°; down, 65°; down and nasally, 50°; nasally, 60°; up and nasally, 55°; up, 45°; up and temporally, 55°.

The visual field efficiency of one eye in per cent is obtained by adding the number of degrees of the eight principal radii given above for the 3/330 white isopter, which normally is 500°, and dividing by 5. For example, if the field is contracted down to 25° in all eight meridians, there would be a remaining visual field efficiency of $25 \times 8 \div 5 = 40\%$, or loss of 60%. If the entire temporal field is lost, the loss would amount to

Up and temporally	55
Temporally	85
Down and temporally	85
Average of up and down (½[45+65]) =	55
	280÷5=56%,

or a remaining visual efficiency of 44%. If the upper nasal quadrant is lost, the loss of field efficiency would amount to 55+52 (average of up and nasal meridians=45+60÷2)÷5=21%, or a remaining efficiency of 79%. Loss of visual field efficiency can be calculated for other field defects in a similar manner.

INTERNATIONAL COUNCIL OF OPHTHALMOLOGY

STEWART DUKE-ELDER, M.D., London

THE INTERNATIONAL Council of Ophthalmology met in Paris, on May 7, 1955. There were present Duke-Elder (president), Berens (vice-president), Hartmann (secretary), Amsler (treasurer), Bietti (International Organization Against Trachoma), Franceschetti (Association for the Prevention of Blindness), Samuels (president of the last Congress), Coppez (president of the next Congress), Arruga (Spain), Charamis (Greece), Palomino Dena (Mexico), Paufique (France), Thiel (Germany), and Weve (Netherlands).

Apart from current business, the following are the most important decisions taken by the Council.

I. "*Index Ophthalmologicus.*"—In accordance with the Statutes of the Council, an "Index Ophthalmologicus" was published at the time of the International Congress in 1954. The sale of the "Index" had, however, up to the present been very slow, involving the Council in considerable expense. It was thought that this was due to the fact that it was insufficiently known. The "Index" contains the names and addresses of ophthalmologists in most countries of the world and information on hospitals, journals, and ophthalmological societies in these countries. It can be obtained at a price of $2.75 from Dr. A. C. Copper, Coehoornsingel 42, Zutphen, Netherlands. Despite the disappointing sales, the Council decided to publish a new "Index" at the time of the Congress in 1958, believing that, once ophthalmologists generally got to know the value of the book, it would eventually become a paying proposition.

II. "*International Dictionary of Ophthalmological Terms.*"—This "Dictionary" is being prepared by Alvaro, Amsler, Bietti, and Duke-Elder, and it is hoped that it will be available before the time of the next International Congress. In the "Dictionary," ophthalmic terms will be translated into six languages: English, German, Spanish, French, Italian, and Latin.

III. *Sub-Committee for the Gonin Medal.*—The term of office of the old committee had expired; the following were elected:

Ex officio members: Duke-Elder, Streiff

Members: François, Friedenwald, Karpe, Müller, and Nordmann

Substitute members: Eliott, Lo Cascio, Malbran, Ida Mann, and Nakamura

IV. *Committee for the Standardization of Colour Vision.*—At its last meeting the International Federation of Ophthalmological Societies had decided that examination of color vision in transport workers should be carried out with the pseudo-isochromatic tables, and for this purpose had initially accepted the Ishihara charts. It was, however, decided that any new tests which appeared from time to time should be recommended if they were considered equally suitable. A committee was

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formed to deal with this matter, consisting of L. C. Thomson (Medical Research Council and Institute of Ophthalmology, London), Yves Le Grand (Collège de France, Paris), Louise Sloan (Wilmer Institute, Baltimore), and J. Zanen (Brussels).

V. *Road Safety.*—A committee, consisting of Bietti, Goldmann, and Dubois-Poulsen, was formed by the Council to study the visual danger to drivers of roadside advertising boardings and the placing of roadside objects at regular intervals. The questions raised were in how far advertisements caused the driver to divert his eyes from the road in the first place, and, in the second, the danger of rhythmic stimulation of the retina in causing nervous symptoms in some persons.

VI. *Congress in Montreal and New York in 1954.*—The *Acta* of the XVII International Congress will be published in three volumes and should appear toward the end of 1955.

VII. The next meeting of the Council will be held in England in the spring of 1956.

Judd St., W.C. 1.

News and Comment

SOCIETY NEWS

Society of Military Ophthalmologists and Society of Military Otolaryngologists.—A joint dinner meeting of the two societies will be held at the time of the annual meeting of the American Academy of Ophthalmology and Otolaryngology in Chicago in October.

Cocktails and dinner will be served at 6:30 p. m. on Oct. 11, 1955, at the Palmer House. The dinner will be followed by a short business meeting.

All members of the Society of Military Ophthalmologists and the Society of Military Otolaryngologists are invited to attend. Application may be made either to Capt. James A. Stokes (MC), U. S. Army, secretary-treasurer, Society of Military Ophthalmologists, Eye Clinic, Walter Reed Army Hospital, Washington 12, D. C., or to Lieut. Col. Frank A. Perri (MC), U. S. A. F., 3650 USAF Hospital, Box 485, Sampson Air Force Base, New York.

PERSONAL NEWS

Lucien Howe Medal Award.—At the meeting of the American Ophthalmological Society, held in June, 1955, Dr. Arthur J. Bedell, Albany, N. Y., was awarded the American Ophthalmological Society's Lucien Howe Medal in recognition of his distinguished service to ophthalmology.

Correspondence

COUCHING OPERATION IN TIBET

To the Editor:—Some time ago I met a traveler who told me of having seen some very interesting photographs of the operation of couching as it was performed in Tibet. I wrote to the photographer, Mr. Tse Ten Tashi, and received from him copies of the photographs, with some descriptive notes and information about the coucher and about himself. I asked and received permission from him to have them published with appropriate credit, as noted. They seem to me interesting enough to be shared.

Although the operation of couching has practically disappeared in Western countries, there are still parts of the world where it will continue for many years. Couching of cataracts is going on all over India, even, I have been told, in cities like Bombay and Madras. It is possible that couchers do more operations than registered doctors. No statistics on this are available. General laws against unlicensed surgery help prosecute these couchers in all states. One coucher who had ruined an eye was given six weeks' rigorous imprisonment recently in Vellore. The state of Madhya Predesh is the only one, so far as I know, where there is a law distinctly prohibiting couching, and there appears to be considerable less couching in this state.

It is difficult to determine by the photographs showing the use of the instruments just what procedure is taking place. I felt it was not right to say any more than Mr. Tashi has said in reference to each photograph. One can assume that the anterior chamber is entered by a keratome-like knife. The zonule is broken and the lens depressed into the vitreous by another dull instrument passing through the first incision. I have never seen a couching operation done, and I have never known a woman coucher.

Although I have not had the privilege of meeting Mr. Tse Ten Tashi personally, I have enjoyed a most pleasant correspondence with him. In response to my request for permission to use the pictures in some publication, he has written the following, which should go with them as a credit note:

"Yes, please use the photographs right and left both in the American papers and Indian papers for the simple reason that precious things are for those who prize them and I have no right to check the advancement of scientific progress. The only thing I want you to do in this connection is to put the following: Photo by Mr. Tse Ten Tashi, Gangtok, Sikkim, Himalayas, India."

Mr. Tashi adds this bit of information about himself:

"He is a leading color photographer in Northern India.

"He is very fond of wild flowers and grows orchids, etc.

"He is the Private Secretary to His Highness the Maharajah Sir Tashi Namgyal of Sikkim.

"I mention these points in case you would like a short description about me."

Mr. Tashi gives the following interesting information about the coucher herself:

"I present photographs of the only lady in Tibet who does eye operations. She is known as Chamy-sangyou, i. e., wife of Chamay Rimpochi (High Incarnate Lama). She is also known as Yang ga la, or Khandru Pema (Lotus of the Angel). She comes from the eastern part of Tibet. Her late husband was a High Lama. She is 45 years old and is renowned over a large area in Tibet. She has taken up many eye operations in Tibet and Bhutan. She does one eye at a time and tries the other if the first one is O. K."

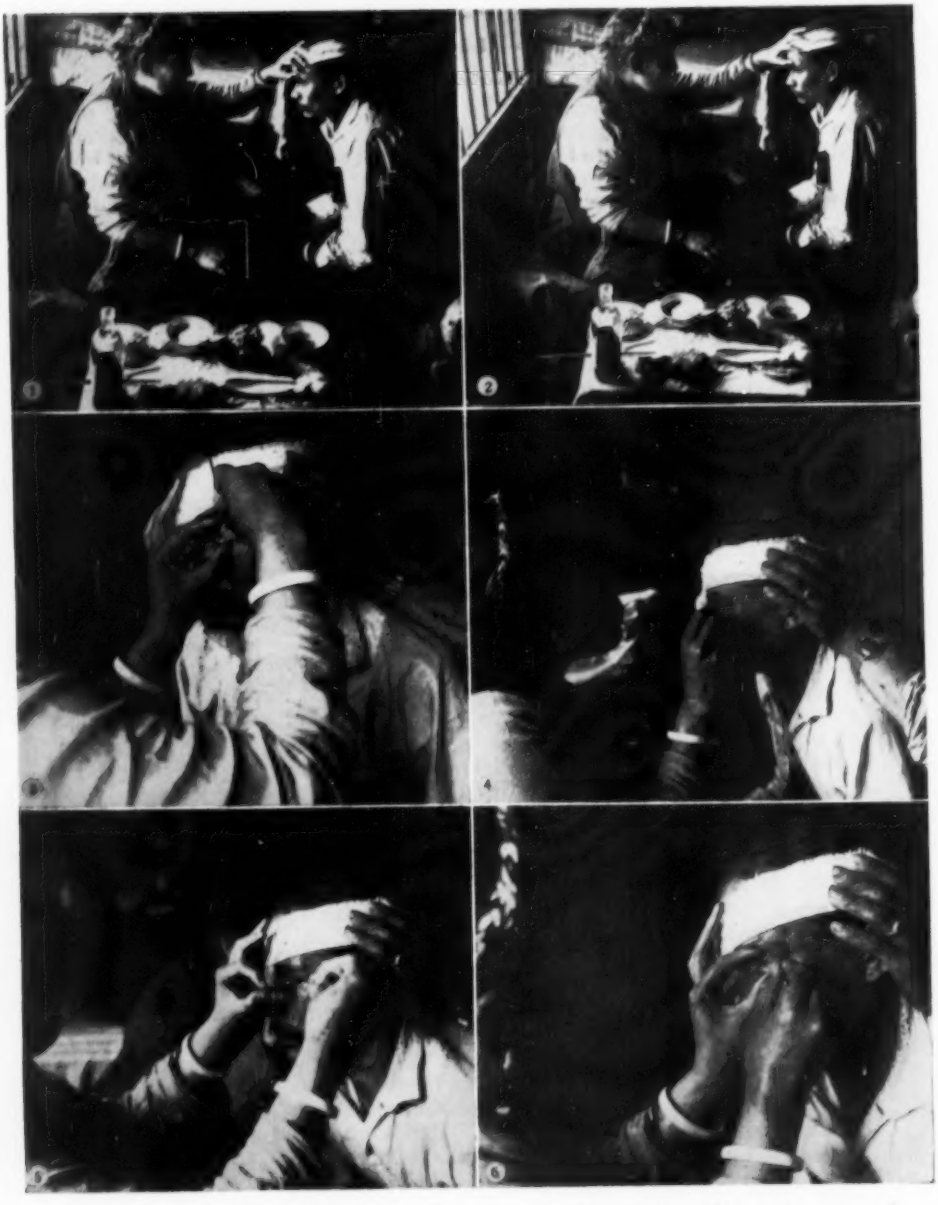
PHOTOGRAPHS AND DESCRIPTION BY MR. TSE TEN TASHI

"(1) Just before the operation.

"(2) The usual prayers to the God of Medicine are offered, as may be seen in the offerings on her table; the lady doctor examines the eye again and again.

"(3) A blunt knife * made in Tibet is being put in.

* Obviously, the knife must be somewhat sharp to penetrate cornea.



"(4) As she put the knife into the eye, she blows with 'Mantras' a sort of 'all success and no pain but new vision to you, O God of medicine, please come out to our help. . . .'

"(5) The position of her mouth shows that it is not an easy task to restore one's lost sight.

"(6) and (7) Twisting of the knife.

"(8) The knife is served round into the eye.

"(9) The knife is being taken out. The water on the face is treated with saffron and must and other powdered herbs of Tibet.

"(10) After the operation his sight is tested and the patient says, 'I can see and know the stuff which you are showing to me.'

"(11) He is again being tested and says, 'Yes, I can count your fingers.'

"(12) A cotton bandage is put round his head. She uses raw, untreated Tibetan sheep wool as dressing, for she finds cotton wool sticky."

VICTOR C. RAMBO, M.D.
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Obituaries

HUNTER SCARLETT, M.D.

1885-1954

Dr. Hunter Scarlett, who practiced ophthalmology in Philadelphia from 1917 to 1939, died at the U. S. Veterans Administration Hospital in Philadelphia on Dec. 23, 1954, at the age of 69.

Dr. Scarlett was born in Erie, Pa., on Oct. 16, 1885, of an English father and a Scotch mother.

After graduating from Erie High School in 1902, Dr. Scarlett entered the University of Pennsylvania and obtained his degree in 1907. He played four years of varsity football and was never taken out of a game for injury. In 1908 he was Walter Camp's choice for All-American right end.

HUNTER SCARLETT, M.D.
1885-1954

Dr. Scarlett graduated from the University of Pennsylvania School of Medicine in 1911, and then interned at the Pennsylvania Hospital.

In 1912 he was appointed Chief Resident of the American Hospital of Paris, and it was in Paris just prior to World War I that he began the study of ophthalmology under Victor Morax—then the Professor of Ophthalmology at Lariboisière Hospital—and later became his assistant. During this time, Dr. Scarlett wrote many articles on research of the eye for *Annales d'oculistique*. One article on a diplobacillus "not yet described," causing corneal infection, was titled "Diplobacilli scarletti."

On Aug. 1, 1914, when war was declared, Dr. Scarlett became a co-founder of the American Ambulance, a large war hospital at Neuilly-sur-Seine, equipped and financed entirely by American funds, although administered by the French government. Dr. Scarlett was immediately appointed Ophthalmologist to the American Ambulance and held that position until he was invalided home, in 1916.

Dr. Scarlett was also appointed Ophthalmologist to the Whitney War Hospital at Juilly-sur-Marne, a branch of the American Ambulance on the Marne battlefield.

In order to operate there, when necessary, he was forced to leave Paris at sundown in an unlighted automobile except for a low red cross on the radiator and drive between shell holes and battle debris. Operating was done there at night with inadequate lighting and equipment, and the return trip to Paris was made just before dawn.

Dr. Scarlett was also ophthalmologist to the "*Phare*," a Paris branch of the New York Light House for the Blind, caring for patients blinded by the war.

In 1916, after two years of acting chief of two war hospitals and assistant at a third, Dr. Scarlett was taken seriously ill with what appeared to be meningitis, but was later thought to be sleeping sickness. He had been caring for a group of Kabile Arabs who were a part of General Gallieni's taxicab army that held the front line during the first weeks of the war.

Dr. Scarlett was invalided to the United States and, after six months' rest, began practicing in Philadelphia.

In 1918, having recovered in health, he volunteered in the U. S. Army and served at U. S. Hospital No. 11 at Cape May, N. J., as assistant ophthalmologist. This was a hospital for brain cases, whose neurologist was Philadelphia's Dr. Charles Frazier.

In 1920, the French government awarded him the Reconnaissance Française.

He was appointed ophthalmologist at Bryn Mawr Hospital in 1920, and held a similar appointment at Pennsylvania Hospital, Philadelphia, until his retirement for reasons of health in March, 1939. During this time he wrote many articles for American ophthalmological journals.

Dr. Scarlett belonged to the following societies: American Ophthalmological Society, American Academy of Ophthalmology and Otolaryngology, Association for Research in Ophthalmology, Philadelphia College of Physicians, and American Medical Association.

In a tribute paid to Dr. Scarlett by the Board of Directors of the Bryn Mawr Hospital was this sentence: "He was nationally and internationally known in his field. He rendered many years of very valuable service to this hospital and to the community and will be greatly missed."

William E. Krewson, 3rd, M.D.

News and Comment

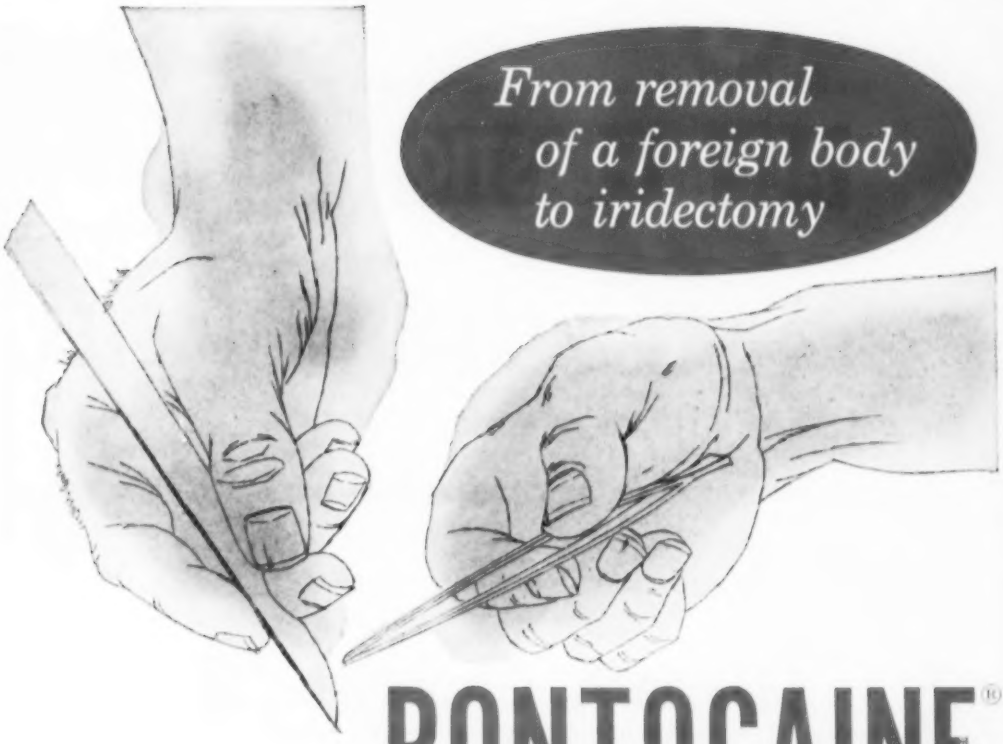
GENERAL NEWS

Ophthalmic Pathology.—In view of the large backlog of eyes in the Armed Forces Institute of Pathology and the resulting delay in the pathologic reports, the Committee on Ophthalmic Pathology of the American Academy of Ophthalmology and Otolaryngology, in conjunction with the A. F. I. P., has made inquiries regarding the facilities in other institutions for processing eyes and so relieving the situation in Washington.

Dr. Michael J. Hogan, chairman of the Committee, has received replies from 26 laboratories in the United States that are able to take on additional eyes in limited numbers. Many of these laboratories have a full load from local institutions but are willing to take on more to relieve the load on the A. F. I. P. and to facilitate earlier reports. All pathologic laboratories need unusual cases for teaching material and are willing to take on an extra load to get them. Ophthalmic surgeons are requested to send human eyes to a nearby laboratory rather than to the A. F. I. P., in Washington, D. C. All the laboratories will be encouraged to refer all important material to the Armed Forces Institute for cataloging and pathologic opinion.

Laboratories in the following institutions will receive and process eyes and report findings and diagnosis:

Institution	Number of Additional Eyes Possible to Process Yearly
Baylor University College of Medicine, Houston, Texas	100
Brooklyn Eye and Ear Hospital	25
Cleveland Clinic Hospital	100
Cornell University Medical Center, New York	25
Doheney Laboratory, St. Vincent's Hospital, Los Angeles	120–150
Emory University School of Medicine, Atlanta	50
Eye, Ear, Nose and Throat Hospital, Pittsburgh	50–75
Grace-New Haven Community Hospital, New Haven, Conn	25
Manhattan Eye, Ear and Throat Hospital, New York	25
Medical College of Virginia, Richmond, Va.	15
Montefiore Hospital, New York	50
Northwestern University Medical School, Chicago	50
Ohio State University College of Medicine, Columbus, Ohio	100
St. Mary's Group of Hospitals, St. Louis	80–100
Stanford University Hospitals, San Francisco	200
Tulane University of Louisiana School of Medicine, New Orleans	50
Medical College of Alabama, Birmingham, Ala.	50
University of California Medical School, Department of Ophthalmology, San Francisco	200
University of Colorado School of Medicine, Denver	50
State University of Iowa College of Medicine, Iowa City	5
University of Kansas School of Medicine, Kansas City	50
University of Oklahoma School of Medicine, Oklahoma City	100
University of Oregon Medical School, Portland, Ore.	50
University of Pennsylvania Hospital, Philadelphia	50
Washington University School of Medicine, St. Louis	75–100
Wayne University Kresge Foundation, Detroit	100



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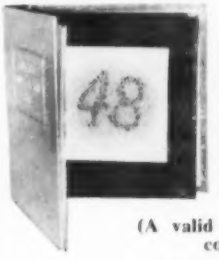

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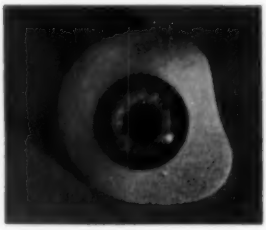

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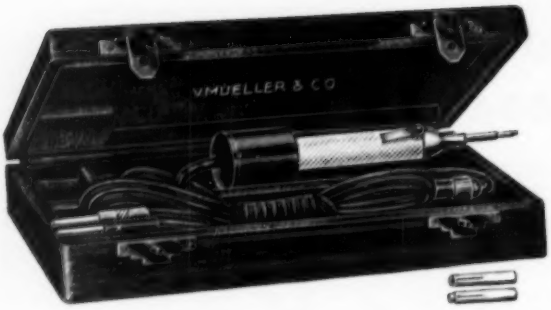

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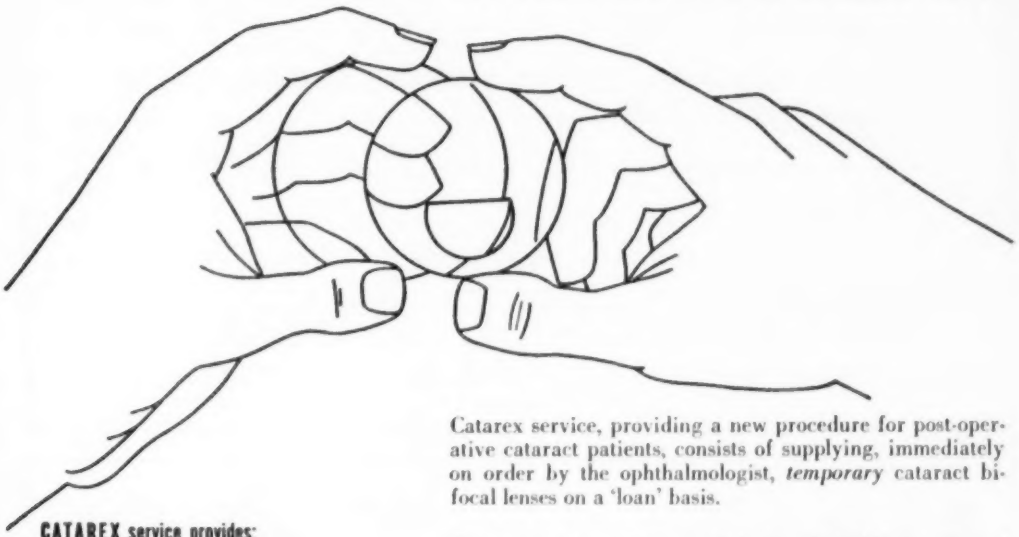

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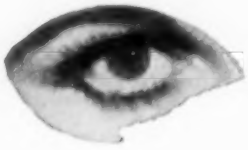

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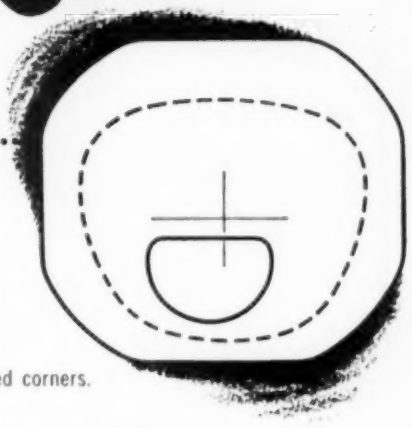
The PC Lens



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Identifiable segment shape — straight top with rounded corners.
Barium crown segment for freedom of color.
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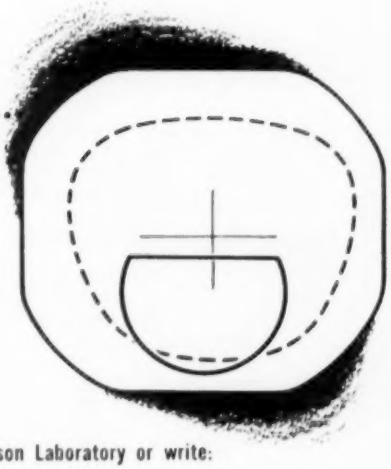
Top line of segment is at an angle for maximum visual comfort.
Also available in tints and trifocals.

The P-28



P-28 Multifocal lens has a 28mm seg. on center, and is available in a 55x60mm semi-finished blank . . . *a multifocal intended to fill every vocational need for large segments at an economical price.*

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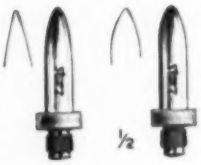

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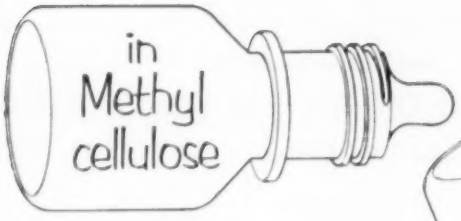

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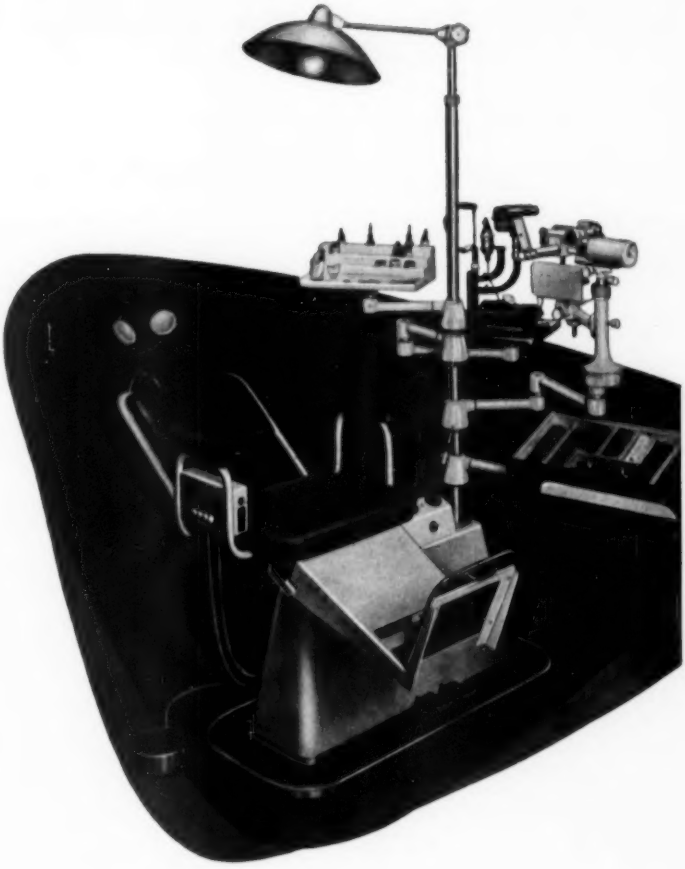

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REFERENCE: 1. Gordon, D.M., *Am. J. Ophth.* **37**:533, April 1954.

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